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ARCHIVES OF DISEASE IN CHILDHOOD

EDITORS
I. A. B. CATHIE and RICHARD H. DOBBS

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MEDICINE AND SOCIAL SCIENCE

THE GEORGE FREDERIC STILL MEMORIAL LECTURE

BY

F. A. E. CREWE

From the Department of Public Health and Social and Preventive Medicine, University of Edinburgh

Everyone of us strives, each in his own fashion, to reach a goal of his own choosing. But since most of the objectives selected are without real or permanent value and since most of us, in our ignorance, choose wrongly, the fortunate among us are, more often than not, they who fail to secure that which they have sought. In each of us a wish for continuance is active; in each of us there lurks a hope that what we do may add significantly to the sum total of the knowledge that in application facilitates the enlargement of human dignity. Every one of us is required to make his contribution towards the well-being of the community of which he is a member and fortunate is the rare individual who from his work derives the maximum of intellectual and emotional satisfaction.

Thoughts such as these are evoked on occasions such as this when we meet to memorialize a man who as an organism underwent dissolution 14 years ago, yet who, as an influence upon thought and action in the field of paediatrics, is still powerful. We are met to refresh our memories of George Frederic Still, once more to pay tribute, minted of deep respect and sincere regard, to one who by the exceptional quality of his personality and of his work rendered outstanding service to mankind, to this Association and to our profession. In the mirror of the dreams of each of us it is his image that we see, for he was what each of us would like to be, a complete man.

That which a man does is what he thinks and what he thinks is the reflection of his ethos and of his own concepts of the nature of the universe and of man's destiny. From the testimony of those who knew him intimately, Still firmly adhered to the Christian faith and modelled his behaviour upon its teachings. From his career, as depicted in his publications, we conclude that he was possessed of an intellectual ability and of a scholarship of more than average quality and that these were exercised with unusual diligence. These qualities in combination are not uncommon within our profession and are not enough in themselves, therefore, to account for Still's exceptional professional and social status. This can only be explained when Still is studied against the background of his time. It so chanced that Still, reaching his professional maturity, entered a particular field of medical interest and activity at a time when this was about to undergo swift enlargement, to encounter in it abundant opportunity for the exercise of his talents. But why did it so happen that he entered this particular field?

We know that from Caius College, Cambridge, where he took his degree in the Classical Tripos with first-class honours, he went to Guy's Hospital, there to become exposed to, and, being what he was, to react to the stimulus that was James Goodhart. It would seem that it was this encounter that gave direction to his ambition. That is how paediatricians are, or should be, made; inclination, unexpressed and possibly unsuspected, becoming revealed as the student reacts to the peculiar attractions of the subject as these are displayed by a teacher who finds in the advancement of his subject deep and abiding satisfaction.

Here I would remark that possibly the greatest contribution a paediatrician can make to his subject is that of attracting to it young men better equipped in respect of general ability than he is himself. Every one of you can provide a reason to explain why you became paediatricians. Some of you may even be able to identify the real reason. In my experience it is far from uncommon to find that a man of outstanding merit in respect of the value of his contributions to his subject is one who at a critical point in his development reacted strongly to the stimulus of a particular teacher. Teachers, like other men, indulge in reproduction and the potent professor is one who begets his own kind. The spoken and the written word can fertilize a mind. If there be a place where eugenic considerations should determine behaviour it is surely in the medical schools. Because we are aware of the potency of words, which can be the very essence of character, we are inclined to restrict our teaching to

technicality although we know full well that this can never be an adequate equipment for those whom we teach, for in medicine knowledge and skill can never be enough; these must be the instruments that compassion and solicitude employ to gain expression. The paediatrician is fortunate in that he deals with the very young, and throughout the animal kingdom these evoke in the adult strong feelings that find their expression in protective action.

Thus it was that Goodhart found continuance in Still, who passed on to The Hospital for Sick Children in Great Ormond Street, with which he was to remain associated for more than 30 years. In 1894, at the age of 26, he published the outcome of his first research. Thereafter, until two years before his death in 1941, a steady stream of papers issued from his pen, these serving to record the history of paediatrics during this period and to show the importance of his own contributions thereto. Still's working life was coterminous with the establishment and early development of paediatrics as a separate field of clinical enquiry and practice. In 1906 he was appointed to the chair of the Diseases of Children at King's College, London, the first of its kind in this country, and in 1928 he was elected as the first president of this Association. In 1933 he presided at the meeting of the International Paediatric Congress in London. He was knighted and appointed as Physician Extraordinary to the King. According to the prevailing standards he was, therefore, a most successful man and the reasons for his success are clearly revealed.

He was genetically well endowed and enjoyed the advantages of a good home and school. He was able to profit from a sound and liberal university education and did so. Entering medicine he chose a calling in accord with his personal attributes, revealed or as yet unexpressed. As a consequence of his encounter with a particular teacher he, being able to respond, reacted to the stimulus thus exerted and entered a field of interest and activity which was about to become closely packed with opportunity for such as he. In his make-up, both genetic and environmental factors operated. He was fortunate in the choice of his parents; he was fortunate also in the choice of the date of his birth, for had he been born 50 years earlier or later the peculiar opportunities for the exercise of his talents which he enjoyed would not have been encountered. Genius is relatively unaffected by time; the commoner general ability which Still possessed required for its expression the environmental opportunity which transmutes the potential into the actual. It is in this sense that each of us is the creation of his environment and since this is ever-changing many able men are denied the chance of discovering the nature and the extent of their ability. The scientist who today enjoys the greatest opportunity for self-expression and who is advantaged over all others in respect of reward is one who 15 to 20 years ago entered the field of physics, being adequately equipped to do so and being fortunate enough to do so. Yet it could not have been foretold then that the greatest demand on the part of the nation today would be for physicists to work in the atomic field. Manifestly an organization that can advise the as yet unconceived is required.

There are three other facets to Still's personality which must attract the attention of those who would model themselves upon him. He developed into a most accomplished public speaker, using words cleverly to bedeck ideas. This acquisition is most valuable when, as in Still's case, the ideas themselves are sound and constructive. With it a man can render great service. Still associated himself with a number of organizations which in their several ways shared his interests and purposes—Dr. Barnardo's Homes, the Society for Waifs and Strays, and the National Association for the Prevention of Infant Mortality. By doing so he extended the influence of medicine upon social affairs and in his own way did much to secure the intelligent collaboration of the general public, without which the efforts of the medical profession must remain largely fruitless. He wrote verse, by means of which he could explore his own mind and reveal his innermost thoughts without the impediment of self-consciousness. In his *Life's Aftermath* there is the complete picture of the man whom, with so much reason, we now praise.

> When I shall die and in the quiet earth
> Am laid to rest,
> Will there remain some breath of aftermath
> Of worst or best
> Some potency of evil or of good,
> Its source unguessed,
> From words or deeds, remembered or forgot,
> A life's bequest?
> God in his mercy grant that all the wrong
> May cease to be,
> Not only be forgotten but blotted out,
> That so of me
> Shall nothing live that might work others ill,
> No legacy
> Of harm to lead one single soul astray,
> —Thus may it be
> When I shall die.

In these lines are displayed the man's humility, his sense of responsibility, his faith, his hopes, the qualities that lay at the root of his actions. He was outstanding as a physician in his day because of his intellectual ability, his diligence, his skill and his

scholarship; but above all else, because he was a man of great charity. From his example every one of us can learn and profit much.

With the passing of time, as those who knew him personally themselves depart, the influence that he will continue to exert will stem in increasing measure from his published books and papers and some of these will become part of the very texture of the subject of paediatrics itself. Ultimately they will come to possess only a historical interest since they deal for the most part with topics the importance of which is already diminishing as knowledge expands and problems are solved to become replaced by others. Happy and fortunate indeed is the man who at the end of his life can say that every one of the several hypotheses he constructed in his younger days, perfectly reasonable and logical in their time, accounting for all that was then known, has been destroyed and replaced, for this means that the the search for understanding has continued to be eager. It means also that the younger men who have succeeded in overturning his conclusions can see further and deeper into the nature of things because they stand on the shoulders of their predecessors. There is great joy to be found in this notion of continuity in the chain of which one may hope to become a link.

Still's books and published papers deal for the most part with clinical, curative medicine in the Sydenham tradition. His interests were entirely in accord with the stage of development that paediatrics had then reached and equally in accord with the needs of the time. In reading those which were readily accessible to me, ample evidence of the acuteness of his powers of observation, of his ability to describe that which he observed and to provide a reasonable explanation of its nature and causes was to be found. Because of my own peculiar interests, I sought for evidence concerning his concepts of disease causation and was greatly pleased when I encountered in his third, and possibly his most permanent, paper on a form of chronic joint disease in children, evidence that he had considered such variables as nutrition, poverty, exposure to insanitary conditions, and the sex of the patient as possible factors in aetiology. I was interested because I wished to discover to what extent Still was aware of the growth of the notions that were ultimately to lead to the inception of two new academic disciplines, those of child life and health and of social medicine.

To me it seems that the development of paediatrics, which, as Still remarks in the introduction of his history of the subject, came to include not only all that is concerned with the sick child, but also the care of the health of the child, at any rate during the first two or three years of life, was together with the development of psychiatry, mainly responsible for the beginnings of a revolutionary change in medical thought and action.

Doubtless a variety of causes operated in the creation of paediatrics as a special branch of medicine. That disease in children presented features peculiar to this age group had been recognized as far back in medical history as Hippocrates himself, but I understand that in this country it was not until about the beginning of the present century that certain opinions had become widely held—that the child was an asset of great worth to the nation, that the high peak of mortality in the first year of life could be removed by the exercise of control over its causal agencies through the application of knowledge then becoming available, and that the specialization in the medical field that was yielding such great harvests of new knowledge and of new power could with advantage be extended to cover the diseases of children. But to my mind the most important aspect of this development was that it implied that it has been perceived that different categories—biological and social—within the population had different medical needs and that for the satisfaction of these different branches of medicine must be developed. Paediatrics was to be the medicine of a biological category. This being accepted, it followed inevitably that there should develop, in relation to this category, a health-promotive aspect of the subject with its emphasis placed upon the medical needs of the healthy child. In the medical field generally this dichotomy into curative and health-promotive divisions has resulted in two distinct organizations—that of the National Health Service, which, in fact, is concerned not with the promotion of health, but with its restoration, and that of the medical services of central and local authority, which in respect of policy are positively health promotive. In the field of child medicine this division is by no means so clear cut. For example, a professor of child life and health may or may not be actively interested in matters relating to the biological category—the child—but he is invariably involved in the diagnosis and treatment of the illnesses of individual children in series. The child welfare clinics of local authority likewise deal with the maintenance of the health of the child as a biological category and as an individual, the lessons learnt from the study of the group being applied to the affairs of the individual and vice versa. It therefore seems to me that this branch of medicine, in its development, is ahead of those branches which deal with the adult. That this is

so is due, in my view, to certain differences that distinguish the mature from the immature, differences which with the passing of time have tended to gain greater emphasis.

In my time the rate and direction of the development of that corpus of knowledge and of that constellation of skills which we know as medicine have, in the main, been determined by discoveries in the physical sciences, by the impact of these discoveries upon medical thought and by the application of the concepts attached to them in medical action. The living organism came to be looked upon as something that could be understood in terms of biophysics and chemistry. The individual came to be regarded as an integrated aggregate of highly specialized component parts, tissues, organs and organ-systems, mutually interdependent and none of them in itself self-sufficient, each making its own particular contribution to the well-being and continuance of the whole. The physical and chemical nature of these various contributions was revealed. Fault in any one of these component parts reflected in its functioning led to the disruption of the whole system. A disease-evoking agency evoked its effects by acting upon a particular component part in such a way as to lead to its malfunctioning. This being the prevailing concept of the nature of man and of disease it followed that diagnostic and therapeutic procedures took the form of attempts to identify the faulty part and to repair its functioning. The profession became particulate in its organization and interests, a particular specialty being restricted to one organ, to one system or to one anatomical region of the body. The inevitable consequence of this specialization was that the patient entering the sphere of the specialist, the hospital sphere, tended to cease to be a person and to become a case. Thus specialization became the dominant pattern of this 'scientific' medicine, in the development of which the hospital evolved as the chief therapeutic and research institution, thus exemplifying in its depersonalized and fractionated services and its highly refined procedures the ideals and principles of the scientific approach to the problem of disease. This specialization has undoubtedly led to great advances in knowledge of structure and function and to great developments in the techniques of diagnosis and therapy. For the specialist of this kind there will always be a place within the medical organization. As a result of the manifest advantages that have resulted from this specialization within the medical profession, a change in the hierarchical order within the profession occurred. In this the specialist ranks high, the generalist low. The medical scientist—physicist, chemist, physiologist, bacteriologist and the like—ranks higher than the clinician.

Latterly, however, there has been spreading the view that medical care stemming solely or mainly from strictly physical and depersonalized considerations is not satisfactory for the reasons that the notions that the individual can be adequately described in physical and chemical terms and that disease is due to the fault in the functioning of a part no longer constitute a working hypothesis that accounts for all the observed facts. The individual is more than an aggregate of harmoniously interrelated specialized parts. He has to be considered not only as an organism living in an external physical environment, but also as a member of a particular society and as the product of a particular culture, for it has been recognized anew that psychological and social factors no less than biophysical play their part in disease causation. It is now remembered that in the magico-religious forms of medicine which preceded our secular scientific variety the medicine man, knowing nothing of the medical sciences, nevertheless was able to achieve much because he paid attention to the bearing of the emotions, attitudes, social pressures and supports upon sickness and health. It is remembered, too, that the great therapists of the past have been those who treated their patients as people responding to complex social pressures. It is not that the clinicians of today are unaware of these things; medicine developed as it did because the physical sciences, nurtured by the needs of a society such as our own, developed earlier and more rapidly than did the biological and the social. The newer function of the almoner and her changed relationship with the clinician are indications that the latter recognizes his need for this particular form of reinforcement. It has been his lack of knowledge of the concepts, content and methodology of the social sciences that has created the opportunity for the almoner to cultivate the view that she is not an instrument used by him for the securing of knowledge of value in diagnosis, therapy and prognosis, but that he and she are partners of near equality.

At this point I must make it clear that many of the opinions I express are tentative. There was a time when to my opinions I personally ascribed considerable value, but with the passing of the years my confidence has waned and I am relieved to find that they are not precious to me, that they have not undergone that strange form of degenerative hardening that transforms opinion into conviction. And so it may well be that my interpretation of events is exceedingly faulty owing to the inadequacy of my knowledge of them. But it does seem to me

that in a few of the branches of medicine, and in paediatrics and psychiatry especially, specialization has not led to the development of a system of thought and action derived almost exclusively from the physical sciences. In paediatrics I suppose that this has been so because of certain differences between the adult and the child as patients. Up to a point, but only up to a point, can the child be considered as an individual organism, for so very obviously he is not independent. The umbilical cord of dependency is not cut at birth; it continues to unite the offspring to its parents for 15 years or more. In a very real sense the sick child is not a sick individual but a sick family and it is within the family, as often as not, that the cause is to be sought and to the family that treatment is given. The family is not merely a small self-contained aggregate of organically interrelated individuals; it is representative of and is the product of a particular form of social organization and of a stratum thereof and, moreover, it is the product of a particular culture. Beliefs fashion attitudes and attitudes behaviour and today there is abundant evidence to show beyond all doubt that in the social structure and in the culture there are to be discovered forces which in their action yield disease. A human being is an integrated unit but one with fears, aspirations, goals, despairs and compulsions which profoundly affect the state of his health, and the line that formerly divided his organic processes from his emotional and social life is now seen to be an artifact.

You, therefore, unlike your professional brethren whose cases need larger beds, have never been able to disregard the psychosocial factors in disease causation and in therapy and so have occupied, and still occupy, a strategic position for the integration of the social disciplines with medicine. This is particularly true today, for recent years have witnessed the swift growth of the behavioural sciences in respect of scientific concept and of skill and there is much deriving from them that has its applications in medicine. In my view it is in the development of this integration of medicine and the social sciences that lies the chance for medicine to make its greatest contribution to society. We as a people are dedicated to the task of building a world from which all the forces that assail human dignity and goodness shall have been eliminated. Preventable disease is regarded as a barrier that must be overthrown. If social and cultural factors make their contributions to the corruption of human perfection these must be identified and brought under control. Since it is upon the profession of medicine that society relies for such action stemming from expert knowledge, it follows that the profession must equip itself with the appropriate interests and busy itself with the acquisition of the relevant knowledge and skill.

To others, if not to you, this must necessarily involve a great extension of the medical sphere since this will come to include problems that transcend the traditional organized medical knowledge that now comprises the equipment of its practitioners. It implies that there must come into being an alliance and collaboration between medicine and those disciplines which are concerned with behaviour from the standpoint of group processes and cultural dynamics. The growth of medicine in the past has taken this very form; the great advances have been the outcome of the fusion of medicine and chemistry, medicine and physics, medicine and mathematics, and the like. In the intellectual field the hybrid produced by the mating of two separate disciplines is remarkable for its vigour.

The practice of medicine must necessarily be conducted within a social setting and involves the establishment by the doctor of such relationship with the patient, and in your case with the patient's family, that cooperation between the two in diagnostic and therapeutic procedures becomes possible. Medicine is one of the series of institutions that together comprise a culture; it has its own corpus of knowledge and techniques, values, beliefs, ideology, rituals and symbols, but they are essentially in accord with those of the other institutions, for example, religion, art, economy, law. In a society such as ours no individual comes into contact with the whole of its culture and so it happens that within the population there are a number of sub-cultural groups. Such matters are self-evident, but their bearing upon the practice of medicine is not.

When individuals belonging to widely different sub-cultural groups are brought into contact, as in the doctor-patient relationship, the efficacy of medical intervention is increased if the doctor is aware of the extent to which the patient's behaviour is influenced by cultural factors and if he is prepared to modify his own procedures so as to bring them into line, as far as possible, with the patient's expectations, which are born of his own concepts concerning himself and his complaint, these in turn being acquisitions from the sub-culture which moulded him. The doctor himself is likewise a socially conditioned person whose intervention takes place in a social system that defines the role he plays and provides the set of values that determines his behaviour. The roles played by 'the way of life', the social organization, the prevailing beliefs, in the establishment of an optimal relationship between doctor and patient are most clearly revealed when a representative of our culture and of its

secular scientific medicine is introduced into an 'undeveloped' country. In his case it is imperative that he should clearly recognize the social and cultural forces that have shaped his thinking and behaving and that he should know sufficient of the social and cultural forces that have yielded his patients, so utterly different from himself. Without such knowledge the value of the service he renders is greatly diminished.

Penicillin and paludrin do not combat the supernatural forces which, according to certain systems of belief, are the real causal agencies of disease. There is no panacea for superstition in our pharmacopoea, yet the terror that can stem therefrom can destroy.

Such knowledge can be, and often is, acquired through experience, but it can be most thoroughly developed through formal teaching in the psychological and social sciences with enough philosophy to enable the student to understand and deal with problems of value judgments.

Medical education to-day almost completely disregards the Hippocratic concern for health; it is essentially a recapitulation of the historical development of 'scientific' medicine during the last four hundred years and its spirit, its basic philosophy and its goal have not changed since Sydenham's time, though its subject matter has become greatly expanded. Its prime purpose is to teach the student to recognize disease, to fit this into a nosological category, and to exhibit the currently appropriate therapeutic action. The student is trained to take his place between the diagnostic laboratories on the one side and the great pharmaceutical manufactories on the other. Disease and death become his pivotal interests. The atmosphere of the hospital and clinic might have been specially designed to obliterate the personalities of those who enter them. The patient, stripped of every identifying symbol and bereft of his group memberships, thus becomes a case of a particular pathological condition. He is an example of a disease rather than a diseased person, that is one suffering from or complaining of disability, pain and anxiety, his behaviour having been changed thereby. Yet in open society it is with people that the doctor must deal.

A discontent with the existing curriculum has been growing rapidly of late and efforts are constantly being made to improve upon it. Unfortunately the overwhelming majority of those involved in these deliberations is composed of medical scientists and of teachers of the clinical subjects whose opinions concerning medical education are all too frequently an expression of preferences in accord with their own personal experience. For the most part they plan to produce scientists and clinicians, better equipped than themselves but accoutred with exactly the same concepts and attitudes. For my part I think that nothing short of a complete change of interest and aim can produce a curriculum in harmony with the needs of the times. It has to be accepted, of course, that because disease is so prevalent the medical student must be so trained that he can play his part in attempts to cope with it by means of accurate diagnosis and skilful treatment. But he should not be encouraged to cultivate the view that it is from such activities that the greatest satisfaction is to be derived, that the cure of disease is his prime function. His reasonable delight in the scientific aspects of pathology and therapeutics should not be allowed to blind him to the fact that disease is the great enemy of achievement and is to be deplored and overcome.

History shows that this revolution very nearly occurred following the First World War, during which the destruction of humanity had been so vast in scale that in this country, as elsewhere, it came to be considered necessary to save life wherever possible. A Ministry of Health was created 'for the purpose of promoting the health of the people' and a number of public health services were initiated for the care of the mother and infant, the school child and the like. But what in fact happened was an extension of the medicine that was; there was no radical change in the purview of medicine; and so it is that the present National Health Service is really nothing more than an extension of that which previously existed, a further expansion of governmental initiative in the medical field.

These events were mirrored in the universities during Still's lifetime. Thus, in Edinburgh, lecturers in the diseases of children were first appointed in 1885 when the subject was recognized by the University. But by 1930, when funds for the endowment of a chair became available, the subject to be professed had become Child Life and Health. To that chair Charles McNeil, then physician to the Royal Edinburgh Hospital for Sick Children, was appointed. Whether or not this change in title from lecturer in the diseases of children to professor in child life and health was in any sense an immediate and significant movement in emphasis from disease to health, from the child as an individual to the child as a biological category, I am not competent to say; but it is certainly true to say that today in Edinburgh the activities of the university Department of Child Life and Health are in accord with its title. Since this is what has happened throughout the universities of the country it can be concluded that the revolution that was threatened but which did not occur in open society has occurred, if not in academic

medicine generally, certainly in your own branch, even though it has not become complete. It is in your branch (and in psychiatry) that the patient is studied as a total person in relation to his total external world. In the psychiatric field it was when the futility and folly of treating a specific disease rather than the whole man was recognized that the subject began to develop.

That there is no academic chair of Adult Life and Health or of Senescent Life and Health is indicative of the present aim, scope and content of medicine and of the bias in medical education. That the hospital ward is the place where medicine is taught is equally ndicative of its aim. I wish to submit that upon those of you who bear titles which include the word health and who are involved in the teaching of the medical student, and therefore in the reform of the medical curriculum, a heavy responsibility is laid. You know that in considerations of aetiology the social milieu cannot be disregarded; you know the extent to which social supports and pressures affect the well-being of the individual; you know the effect of ethnocentrism upon judgment; you know that the doctor-patient relationship must be extended to one of doctor and community; you know how unwarranted is the assumption that reason is the controlling and determining force in human behaviour and that emotions, customs, cultural patterns and other non-rational factors cannot be disregarded when seeking diagnostic information. You know that the notion of a fixed innate human nature, common to all, is utterly mistaken and that different sub-cultural groups within the population have cultivated different patterns of response to the same situation. You have reason to know these things better than most of your colleagues active in other fields.

If then, in your case a certain knowledge of sociology, social psychology, cultural anthropology, demography, for example, is or would be of considerable advantage to you, you can be certain that it would be of equal advantage to all within the general field of medicine. If this be so, then the question arises as to the means and methods that require to be made available. In the modern world most problems are complex and require for their investigation a combination of disciplines. At the level of W.H.O. problems relating to health and disease are tackled by teams which are composed of medical and social scientists. In many of the American medical schools social scientists are members of the medical faculty and in conferences of this kind social scientists regularly participate. I doubt very much that such an arrangement is entirely satisfactory; there are certain difficulties. It is very rare, as yet, for a social scientist to become interested in problems with medical aspects of major importance. The cultural anthropologist, for example, is much more likely to be interested in and to know more of Polynesia and the quaint customs of its people than of Pimlico. Moreover, these social scientists, like ourselves, have developed a technical language comprehensible only to themselves so that intercommunion tends not only to be difficult but even misleading, for words used by them and by us are given different connotations. Certainly, if an alliance is to become effective, medical and social scientists must live and work together if they are to comprehend each other's concepts and methodologies.

Personally I should prefer that these subjects should be taught by medically qualified teachers who had specialized in them whilst members of the staff of a department of social medicine, where these subjects can most appropriately be accommodated. Be this as it may, what matters is that the student of medicine should be brought into contact with these subjects offered as part of the medical curriculum itself. This would not necessarily mean that to an already overloaded curriculum still more would be added. If the curriculum were reorientated a good deal of that which is now included could be discarded. Moreover, if the student's education was organized around the central theme of health as a prerequisite to achievement, learning would surely become more meaningful and therefore easier, as would also teaching.

I now must make an end to what to me has been somewhat of an ordeal. You will understand that it is quite impossible for anyone to decline an invitation to deliver a memorial lecture of this kind. It is a great honour to be permitted to occupy this position. It is also a challenge that must be accepted. To be selected by one's peers is to be loaded with a responsibility that cannot be shirked. I ask you to overlook my deficiencies, remembering only that I am both proud and grateful to have enjoyed the privilege of joining with the members of this Association in this ceremony of remembrance of a man who in his day was much concerned with medical education and who would most certainly have been aware of the urgent need for a new outlook. So much reliance is now placed upon medical opinion by those who translate recommendation into action directed towards human betterment and social amelioration that at no time in history has it been more important that this opinion should be soundly based on knowledge as comprehensive as possible.

MONGOLISM IN AFRICANS

BY

JOSEPH LUDER and LATIMER K. MUSOKE

From Mulago Hospital, Kampala, Uganda

(RECEIVED FOR PUBLICATION MARCH 28, 1955)

It has been generally believed that mongolism is very rare among peoples of negro stock, and some authorities even go so far as to deny its existence among Africans, although conceding a greatly reduced incidence compared to that of white races among negro communities living as minorities in white countries.

The absence of any published reports of mongolism in Africans, and the clinical experience of psychiatrists working in Africa have strengthened this belief. The series of 173 cases of mental illness, analysed by Tooth (1950), in the Gold Coast contained no examples, and Carothers (1953) was unable to find a single case or even hear reports of any after a long experience of psychiatric conditions in East Africa. On these grounds he states categorically that the condition does not occur among negroes in Africa, and postulates that there must, therefore, be some noxious influence on foetuses of the white races in the early weeks of intrauterine life which those of negro stock escape.

This paper reports five cases of mongolism seen in the vicinity of Kampala among the indigenous peoples in the space of one year, and suggests reasons why the conditions may have been frequently missed in the past. Four of the cases were seen at routine paediatric out-patient attendance at Mulago Hospital, Kampala, and one other at a welfare clinic near Kampala. No other form of selection was used.

Case Reports

Case 1. A female Ganda child was born in July, 1953. She was born after a normal full-term delivery, and was breast fed. In spite of adequate breast-milk she thrived poorly, and was afflicted with snuffles and occasional coughs. Cyanosis was noticed in the early months of life. By the age of 14 months she had only just begun to sit and made no attempt to stand. She was not able to say any recognizable words.

The parents had been married for nine years before the birth of this child. There were no previous children, but one miscarriage had occurred in the early years of the marriage.

The mother's age was given as between 30 and 35, and the father's as about 35.

On examination she was an undersized, underweight child, who could barely sit up unsupported. She was a cheerful child, who was constantly moving and groping with her hands. Cyanosis was marked in the palms and soles, and to a lesser extent in the nails. The facies were typically mongol (Fig. 1) with slanted eyes, depressed bridge of the nose, and prominent tongue, which was pointed when protruded. The skull was of normal shape, and at 14 months the anterior and posterior fontanelles were closed. There was no sagittal fontanelle

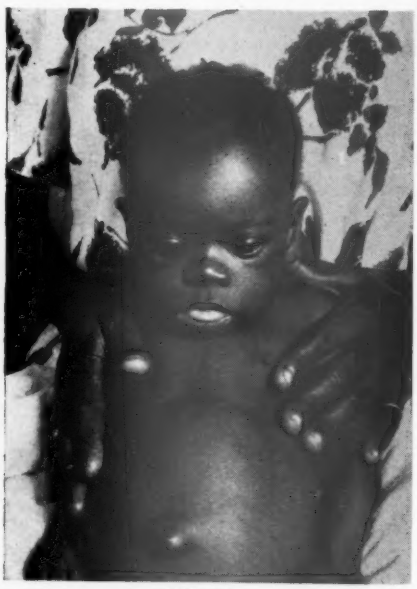

FIG. 1.

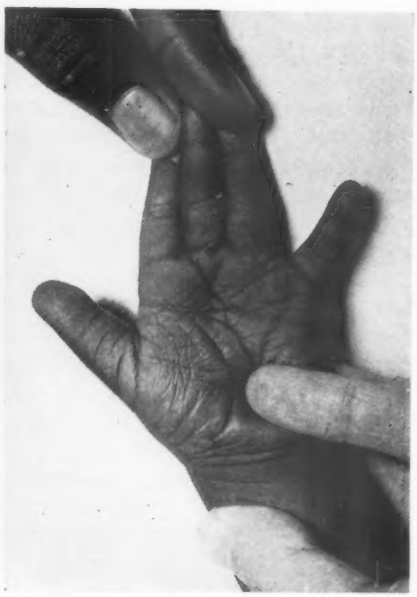

FIG. 2.

and the sagittal suture was not obviously separated. The hands showed typical short little fingers and a transverse crease (Fig. 2), but the palmar ridges were poorly developed, and the position of the tri-radii could not be made out. The first and second toes were widely separated, with a moderately deep cleft between them.

There was considerable enlargement of the heart clinically and radiologically, with a loud systolic murmur to the left of the sternum, maximal in the third intercostal space. No thrills were present.

The child was markedly hypotonic, but there were no other abnormal signs in the nervous system. An umbilical hernia was present.

The mother's palmar tri-radii showed a normal angle.

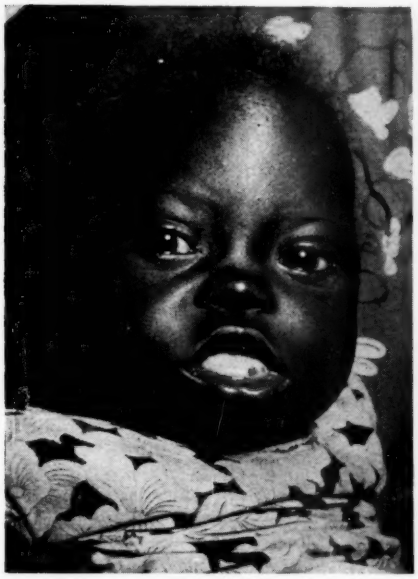

FIG. 4.

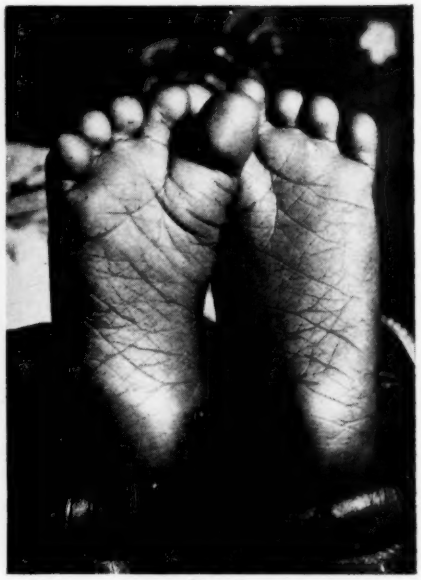

FIG. 5.

Case 2. This was also a female Ganda child born in February, 1954.

She was a premature child of unknown birth weight. Breast feeding had been complemented with diluted cow's milk from birth. The child always appeared weak and thrived very poorly. She was brought up for advice at the age of 8 months because of general weakness and several recent attacks of diarrhoea.

There were three previous normal children. The gap between the patient and the next eldest child was 10 years.

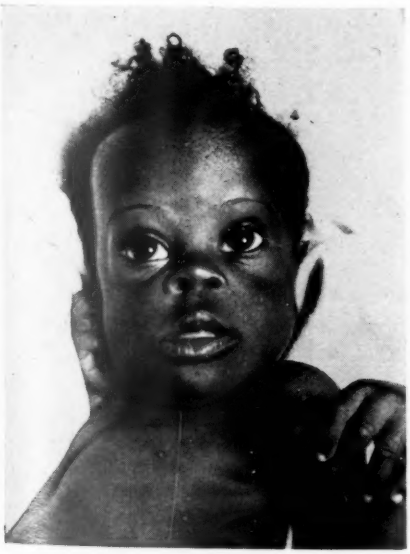

FIG. 3.

The mother's age was given as 39, although she looked older. The father's age was not known.

On examination she was grossly underweight (weight 8 lb. 1 oz.) lying limply in her cot and showing few movements. The nose was very small, with a depressed bridge, and the eyes were slanting. The epicanthic folds were marked (Fig. 3). The tongue was frequently protruded.

Palpation of the skull revealed separation of the sagittal suture, a sagittal fontanelle and a patent anterior fontanelle. The posterior fontanelle was closed.

The little fingers of both hands were short and incurving, but the tri-radii could not be clearly made out. The great and second toes were widely separated, with a wide plantar cleft between them. A small umbilical hernia was present.

Hypotonia was very marked in all limbs, and the child was unable to life up her head.

Attempts to interest her in toys produced little response.

Case 3. A female Lango child was born in December, 1953.

She was breast fed and thrived well. There were several attacks of upper respiratory infection in the early months and one of bronchopneumonia.

There were five siblings, of whom one had died. The ages of the parents were not known.

She was seen at the age of 9 months, and was a plump child, weighing approximately 17 lb.

She had a typical mongol facies, with slanting eyes, small button nose and small ears (Fig. 4). The tongue was large, smooth, protuberant, and had patches of pigmentation at the tip. She had marked snuffles.

In the skull, the anterior fontanelle was large, admitting three fingers, and the posterior fontanelle was closed, but about 1 cm. in front of the latter was a small depression admitting the tip of a finger.

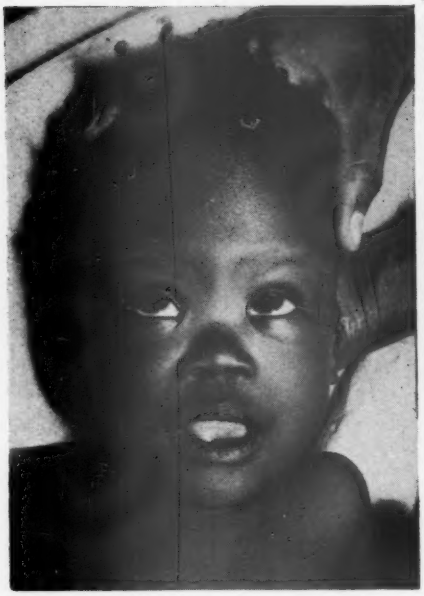

FIG. 6.

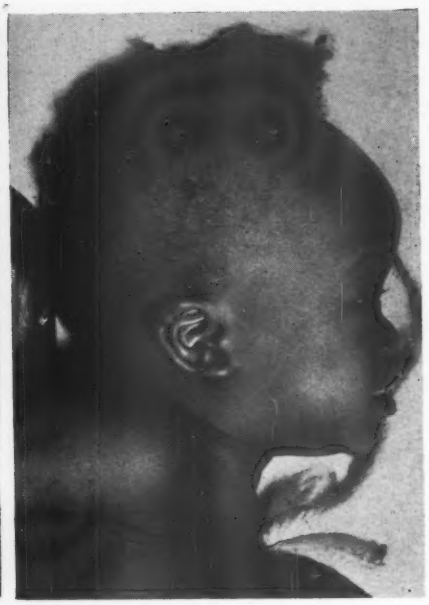

FIG. 7.

folds, a prominent, frequently-protruded tongue which tended to be pointed, and low-set ears with irregular helices (Figs. 6 and 7). Marked snuffles were present.

In the skull, the anterior fontanelle was very large, admitting four finger-tips easily, and there was a patent sagittal admitting one finger-tip. The sagittal suture was slightly widened, and the posterior fontanelle was closed.

The little fingers were short and in-curved and showed only one transverse crease (Fig. 8), but the tri-radii of the palms could not be made out. In the feet, the big and second toes were widely separated, but there was no well-marked plantar furrow (Fig. 9).

The little fingers were short, not reaching to the distal crease of the fourth fingers, and in the palms the transverse creases were coalesced into a single furrow. The proximal tri-radii of both palms were displaced distally forming the typical obtuse angle with the distal tri-radii.

The great and second toes were widely separated and a furrow was present in the sole between them (Fig. 5).

She was just able to sit up for a few seconds, but showed little interest in the surroundings and did not grasp objects offered to her.

The other systems were normal.

Case 4. A male Ganda child was born in January, 1954.

He was breast fed but thrived well only for the first three months of life. He was first seen at 3 months of age, having had snuffles from the early weeks, and having developed a bulging of the sternum. In succeeding months he had frequent attacks of pyrexia and cough, and the weight gain was very poor.

There were four siblings, all well and mentally normal.

The mother's age was given as 28 to 29, and the father's as 32.

On examination, aged 9 months, he was a thin underweight child, weighing only 11 lb. 8 oz. The facial appearance was typically mongol, with slanting eyes, marked epicanthic

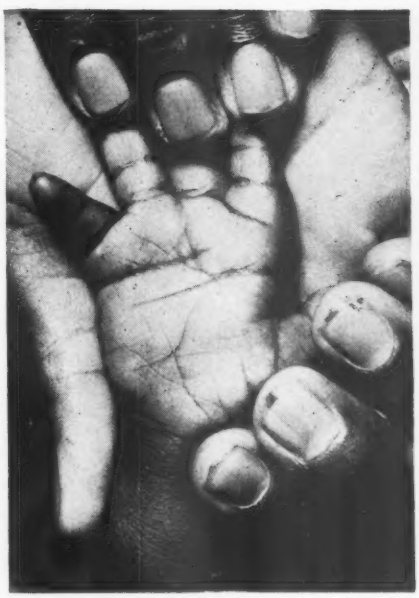

FIG. 8.

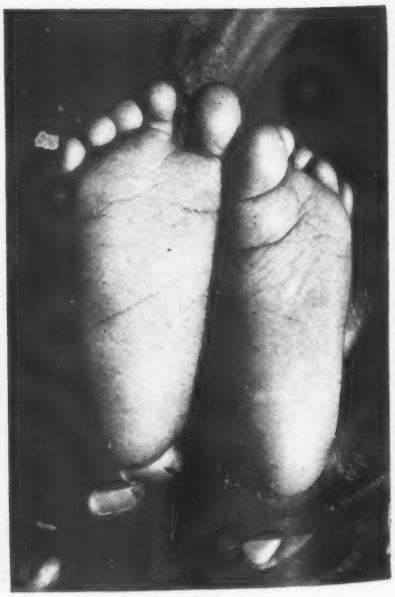

FIG. 9.

The child was not able to sit up unsupported, and showed little tendency to use his hands in a coordinated fashion. He would hold a biscuit in his hand, but would not put it to his mouth, and soon tended to drop it. All limbs were markedly hypotonic.

Other systems were normal.

Case 5. A male Lango child was aged 1 year 2 months.

His early history was not known, and he was brought to hospital suffering from lobar pneumonia. Further questioning revealed that he was unable to stand even

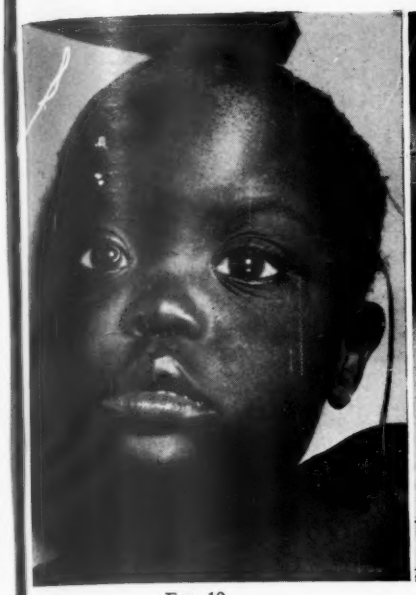

FIG. 10.

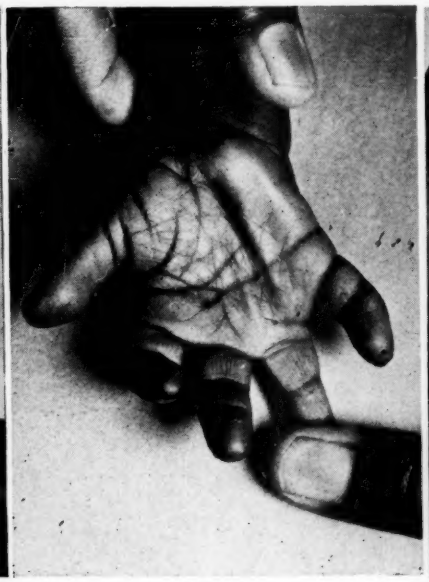

FIG. 11.

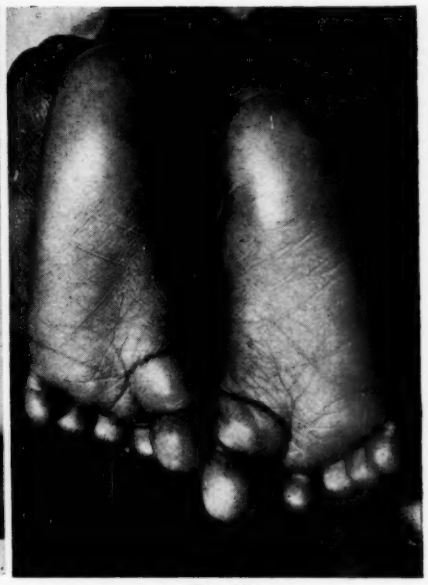

FIG. 12.

with support, and said no recognizable words. He did however, hold objects in his hands and transfer them from one to the other.

There were two older siblings, aged 6 years and 4 years. Both were mentally normal.

The parents' ages were not known.

On examination, the facies were suggestive of mongolism, although not fully characteristic (Fig. 10). The eyes were widely spaced and slanting, although the epicanthic folds were not prominent. The tongue was of normal size and not protuberant.

In the skull the anterior and posterior fontanelles were closed, but there was a patent sagittal fontanelle.

The little fingers were very short and in-curving and possessed only one transverse crease, with a rudimentary second crease (Fig. 11).

There was very wide separation of the big and second toes with a deep plantar furrow (Fig. 12).

Other systems were normal.

Discussion

It is accepted that there is no single diagnostic criterion for mongolism, and that many of the characteristic features can be found from time to time in normal individuals (Penrose, 1954). Each of these characteristics, however, occurs with vastly greater frequency among mongols than among the general population, and a concentration of several of these factors in one individual would put the diagnosis beyond reasonable doubt. Among these characteristics Penrose (1954) lists epicanthic folds, fissured tongue, transverse palmar flexion creases, lax ligaments, short stature, high cephalic index, in-curving minimal digits and the dermal-ridge sign.

Some of these features are not recognizable at birth or in the early months of life, for instance, dermal-ridges or a fissured tongue (Carter and MacCarthy, 1951), and conversely a third fontanelle is a valuable though not pathognomonic sign in early infancy (Carter and MacCarthy, 1951; Hoyle and Franklin, 1954).

Table 1 sets out the frequency of nine typical features of mongolism in our cases, and it can be seen that four of the cases showed six or more features and one case showed four. This last case, although seeming perhaps to be disqualified, was

TABLE 1

THE DISTRIBUTION OF NINE TYPICAL MONGOL FEATURES IN THE CASES

Case	Age (mths.)	Slanting Eyes	Epicanthic Folds	Protuberant Tongue	Patent Sagittal Fontanelle	Short Fifth Digit	Separation of Toes	Hypotonia	Mental Retardation	Tri-radius Sign
1	15	+	−	+	−	+	+	+	+	−
2	9	+	+	+	+	+	+	+	?	−
3	11	−	−	+	+	+	+	−	+	+
4	11	+	+	+	+	+	+	+	+	−
5	14	−	−	−	+	+	+	−	+	−

nevertheless recognized as a mongol at first sight by several colleagues, and there is no doubt that the facial appearance of mongols can be appreciated without always being capable of full analysis.

Apparent Rarity. How true is the widely-held belief that mongolism occurs much more rarely among negro peoples than among the white races? Published evidence on this point is contradictory. The views of Tooth (1950) and Carothers (1953) have already been mentioned and to these must be added the work of Thompson (1939) who found, in a large survey of mongolism in the U.S.A., that whereas negroes form 9% of the total population of the country, they supplied only 1% of all the mongols. These authors, however, were concerned mainly with case material of ages ranging from the middle years of childhood upwards. Tooth's 173 patients, for example, were all adults, and Carothers dealt with a mixed, mainly mental hospital population. Of perhaps greater significance, however, is the experience of Jelliffe (1954) who failed to find a single case during an extensive paediatric experience in Nigeria. This author concludes from this that where mongolism is to be found among the negro races, as in the U.S.A., it is due to the admixture of Caucasian strains.

There is little doubt that a more accurate estimate of the incidence of mongolism is obtained by surveys among newborn infants and infants. Where this has been done a different picture emerges. Thus Parker (1950), examining the records of 27,931 live-births, found 29 mongols among 25,025 negro infants, an incidence of 1·16 per 1,000, and 3 mongols among 2,905 white infants, an incidence of 1·03 per 1,000. This difference is not statistically significant. These figures are rather lower than those given in other smaller series (Carter and MacCarthy, 1951; Benda, 1946), the difference being probably due to the difficulty of diagnosis at birth, and the large number of observers necessarily involved in such a large series. Benda (1946) states that possibly as many as 50% of mongol babies may be missed at birth. Important evidence is forthcoming from South Africa. Kahn (1955) says that about three cases are diagnosed each year among 3,000 African live-births, approximately the same incidence as at a neighbouring European maternity hospital.

It is clear, therefore, that the incidence must appear widely different in various regions of Africa. Much of the rarity is more apparent than real. The diagnosis will obviously be made much more rarely where obstetrical and paediatric services are few or absent. During the early months of life, the depressed nasal bridge and invariable snuffles of the mongol must frequently lead to a misdiagnosis of congenital syphilis. Mongols are nearly all stunted in height and thrive poorly during the first few years of life (Benda, 1946), and must often be considered as cases of malnutrition. This may, indeed, be superimposed as a result of the difficulty of feeding a mentally retarded child. Where a congenital heart accompanies the condition this may often obscure the underlying diagnosis.

Few mongols must see the light of day after the early years of life. They suffer a high mortality in childhood, estimated by Tredgold (1947) as 80% during the second half of childhood. A slightly lower figure is arrived at by comparing the incidence at birth of 1 : 669 live-births found by Carter and MacCarthy (1951) and that of 1 : 2,000 among school-children of between 10 and 14 years found by Penrose (1949). This mortality would be increased by the very high infant mortality in Africa.

Those who survive are generally amiable and quiet imbeciles, the majority able to walk and talk. Among primitive and illiterate communities they either probably escape detection as mental defectives, or are hidden away as objects of shame. In any case, where mental hospitals are few, the available beds will be reserved for dangerous or violent psychotics rather than the placid mongol. It is striking that among the 173 random examples of mental hospital inmates studied by Tooth (1950), mental defectives numbered only six.

Diagnosis. It is not the intention here to give full details of the diagnosis of mongolism; this has been covered fully by other authors (Tredgold, 1947; Benda, 1946). Certain difficulties, however, are met with in making the diagnosis in African children. The broad nose with depressed bridge of the negroid face will, to some extent, mimic the button nose of the mongol. Marked epicanthic folds do not occur as commonly as in European mongols, nor, in this small series, did it appear that a flattened occiput was so often seen. On the other hand, widely separated first and second toes, with a deep plantar cleft, was noted in all cases. Hypotonia is a less reliable sign in African cases because of the frequency of a much more widespread cause, namely, malnutrition. In the early weeks of life, when the diagnosis ought to be made, reliance must be placed on the skull signs, in particular a patent sagittal fontanelle and separated sagittal suture, a short in-curving little finger, often with a single transverse crease, slanting eyes and a protuberant pointed tongue. It must be emphasized that it is

a combination of a number of signs which makes the diagnosis.

Incidence. It is also possible, however, that the true incidence is indeed somewhat lower among African races, and probably other communities also, where the average age of mothers is low. Maternal age is widely accepted as being the most important aetiological factor (Penrose, 1954; Carter and MacCarthy, 1951). The latter authors show that at the end of child-bearing life the incidence is twenty times that at the beginning. With this point in mind, we have examined the ages of all mothers delivered in Mulago Hospital, Kampala, in 1953.

Bearing in mind that the figures are somewhat vitiated because of the limited knowledge of ages among backward peoples, the following points emerge: (1) Out of 1,176 maternities only six occurred over the age of 40, and only 41 over 35 (3·6%). (2) Mothers under the age of 25 numbered 63·4% of all mothers delivered, while those over 30 numbered 14·6%. Comparable figures for England are provided by the Registrar-General's Statistical Review for England and Wales (1947) quoted by Carter and MacCarthy (1951). There, mothers under 25 formed 29·1% and mothers over 30 formed 40% of all maternities. Those over 35 formed 17%. There is, thus, a considerable concentration in the African mothers towards the younger end of fertile life. These results are set out in Fig. 13.

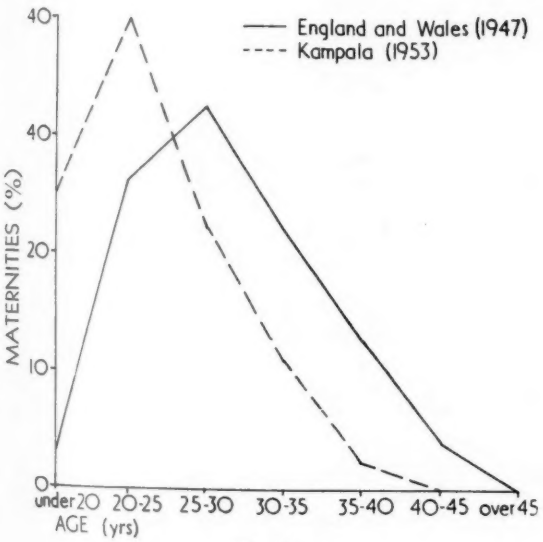

FIG. 13.

It would be interesting to see the results of a similar survey in Nigeria, in view of the probable rarity of mongolism there. At any rate it seems to be beyond question that the occurrence of the condition among the indigenous Ganda and Lango peoples of Uganda cannot be explained by the infusion of Caucasian blood.

An accurate estimate of the true frequency of the condition in this region must obviously await a large field survey. Meanwhile, it is permissible to conclude that the condition occurs in African races, possibly less often than among more advanced communities. With the increase in education, which is likely to raise the age of marriage for women and thus the age of motherhood, and with improvement in nutrition, which is likely to increase fertility, it seems that an increase in the incidence of mongolism must be anticipated.

Summary

Five cases of mongolism are reported from the Ganda and Lango tribes in the vicinity of Kampala. The condition is more common than has been believed from the great infrequency of the diagnosis in the past, but it is probable that the true incidence is still lower among Africans than among European peoples.

Thanks are due to Drs. H. C. Trowell and Hebe Welbourn for permission to quote details of cases under their care; to Professor C. Rendle-Short for access to obstetrical records for 1953; and to Dr. H. C. Trowell for his advice and help. We wish to thank the Hon. the Director of Medical Services, Uganda, for permission to publish.

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FAT ABSORPTION STUDIES IN THE DIAGNOSIS AND TREATMENT OF PANCREATIC FIBROSIS

BY

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The presence of steatorrhoea in pancreatic fibrosis was formerly the cause of its confusion with coeliac disease. This confusion was dispelled by the studies of Blackfan and Wolbach (1933) and of Andersen (1938) who clearly separated pancreatic fibrosis as a separate entity by showing that in this disease there was atrophy of the secretory tissue of the pancreas and that the steatorrhoea resulted from deficiency in pancreatic lipase. Andersen (1945) claimed that, although analysis of single stools or three-day stool collections generally revealed a great increase of faecal fat in pancreatic fibrosis, this was not always found. In the light of recent work, however (Kamer, Bokkel Huinink and Weyers, 1949), it would appear that fat balance studies are necessary for a reliable assessment of fat absorption.

In the treatment of pancreatic fibrosis Andersen (1949) stressed the importance of maintaining satisfactory nutrition and claimed that the respiratory involvement, which is such a common feature of this disease, might be secondary to impaired absorption of some substance essential for the normal functioning of the bronchi. The value of pancreatin in improving absorption of food substances in pancreatic fibrosis has been studied by various workers. Shohl, May and Shwachman (1943) found that although pancreatin resulted in a reduction of faecal nitrogen there was no significant decrease in faecal fat, whereas Andersen (1945) using a pancreatin preparation of higher lipase content than that employed by Shohl *et al.* showed that it produced a considerable decrease in faecal fat. May and Lowe (1949), however, have questioned the usefulness of pancreatin in the treatment of this disease.

The object of the present study was to ascertain the magnitude of the fat absorption defect in pancreatic fibrosis by means of fat-balance studies and chylomicrographs, and to compare the findings with those obtained in coeliac disease. From the fat absorption findings in pancreatic fibrosis an attempt was made to estimate the value of pancreatin in treatment and to place dosage on a rational basis.

Materials and Methods

Clinical Material. This comprised 22 children with pancreatic fibrosis, aged from 2 weeks to 5 years, who were studied in the Children's Hospital, Birmingham. The diagnosis was established by the absence or marked reduction in duodenal juice of the pancreatic enzymes, lipase and trypsin, or by necropsy findings. Eighteen children under 5 years of age with coeliac disease were investigated in the hospital during the same period. The diagnosis of coeliac disease was made before treatment with a wheat gluten-free diet by the investigations described by Anderson, Frazer, French, Gerrard, Sammons and Smellie (1952). These investigations were repeated after the children had received this diet for three to six months. The results of the fat-balance studies and chylomicrographs in the children with pancreatic fibrosis have been compared with those in the patients with coeliac disease both before and after treatment with a wheat gluten-free diet.

Pancreatic Enzymes. The enzyme estimations were made on three separate samples of duodenal juice from each intubation, and the average values obtained.

Lipase was measured by the following method: to 5 ml. phosphate buffer containing 0·5% bile salts, at *p*H 7·8, in a 50-ml. stoppered conical flask was added 1 ml. of acid-free olive oil and 0·1 ml. of duodenal juice. The mixture was shaken for 30 minutes at 37°C., acidified, extracted with 20 ml. benzene and 10 ml. of the upper benzene layer was titrated with 0·05 N tetramethylammonium hydroxide in alcohol. The titration figure in ml. gave the units of lipase per 0·1 ml. duodenal juice (Frazer and Sammons, 1955).

Trypsin was estimated by the method described by Tomarelli, Charney and Harding (1949) using azoalbumin as substrate.

In 20 'normals', that is children who were not suffering from steatorrhoea, the range of lipase in 0·1 ml. duodenal juice was 1·2 to 5·5 units (mean 3·2 units) and the range of trypsin in 1 ml. duodenal juice was 3·4 to 27 units (mean 13 units).

Fat Absorption. A fat balance was carried out on each child for a minimum period of five consecutive days, with the exception of eight children with pancreatic fibrosis who were too ill for metabolic studies. For this purpose the patient received a known dietary fat intake, 20 to 50 g. daily according to age. The stools were collected daily, a metabolism bed being used for infants or when the stools were loose. Estimation of the faecal fat was carried out by a modification of the fatty acid method of Kamer *et al.* (1949). The daily totals of faecal fatty acids were converted to three-day sliding means to minimize sampling errors, and the mean percentage fat absorption for the period obtained. In normal children, fat absorption is over 90% of the fat intake (Gerrard, Ross, Astley, French, and Smellie, 1954).

Systemic Hyperlipaemia. This was investigated by means of the chylomicrograph technique described by Frazer and Stewart (1939). A specimen of blood was taken from the fasting child into a capillary tube. A meal containing 5-20 g. fat, depending on age, was then given; the standard meal for the infant consisted of a National dried milk formula; for the older child the fat was contained in milk, butter and eggs. Specimens of capillary blood were taken at hourly intervals after the meal, up to five hours. The specimens of blood were allowed to clot, one end of each tube sealed in a flame, and the tubes then centrifuged for five minutes. A drop of the serum was placed on a microscope slide, covered with a coverslip, and examined under a microscope with dark-ground illumination. The number of bright, mobile particles in a standard field (a square 0·5 cm. × 0·5 cm.) were counted, and the average of three fields taken. From these counts, the maximum chylomicron increment, i.e. the greatest increase in fat particles above the fasting value, was obtained for each patient. By this method the maximum increment in each of a series of 18 'normal' children under 5 years of age was always over 150 particles.

Pancreatin. The pancreatin used in the present study was obtained from one firm only (Paines and Byrne, Ltd.). Initially it was used both as powder and as granules with a coating to prevent destruction of the enzyme activity by the acid gastric juice; it was then our custom to give powder to infants receiving a milk formula and granules to older children. We found, however, that granules gave very irregular fat absorption figures, probably due to the differing solubility of the coating, and so subsequently we gave the powder to our older children also. Both 'single' strength and 'triple' strength pancreatin were used. We found that 0·05 g. of 'single' strength powder contained 5·7 units of lipase and 14 units of trypsin, a lipase to trypsin ratio of 1:2·5. As the mean figures for the trypsin and lipase content of 1 ml. duodenal juice from the 'normal' children were 32 units and 13 units respectively, this gave a lipase to trypsin ratio of 1:0·4. It is thus evident that pancreatin powder is relatively low in lipase compared with normal duodenal juice. In terms of volume of normal duodenal juice, 1 g. of 'single' strength powder had lipase activity approximately equivalent to 3·5 ml. and trypsin activity approximately equivalent to 21·5 ml.

The pancreatin was administered in cold or lukewarm milk (temperature below 37°C.). For infants receiving a milk formula the powder was mixed with the feed; for older children it was mixed with a little cold milk and given in the middle of the meal. Our routine was to give the child a small dose of pancreatin, e.g. 0·5 g. 'single' strength per feed, and after three days a fat balance was carried out, and the mean fat absorption on that dosage was obtained. The dose was then increased by 0·5 g. or by 1 g. until the mean fat absorption showed no further increase. 'Triple' was substituted for 'single' strength when the dosage of the latter reached 2 g.

Results

Pancreatic Enzymes. Estimation of the lipase and trypsin content of duodenal juice was carried out in 17 of the children with pancreatic fibrosis. From Table 1 it will be seen that trypsin was completely absent in all but two (Cases 4 and 14), aged 10 weeks and 2 years respectively. The enzyme estimations were subsequently repeated when these two children were 11 months and 3 years old respectively. Pancreatic trypsin was then completely absent in both, which would suggest that in these two children atrophy of the secretory tissue of the pancreas had been progressive. Small amounts of lipase were detected in seven children, five of whom had no trypsin. Although this might indicate that complete suppression of pancreatic lipase occurs at a later age than that of trypsin, it is possible that the small amounts of lipase obtained might have been extrapancreatic in origin and might depend upon the level of duodenal sampling.

The range of these enzymes in the duodenal juice of the children with coeliac disease was lipase 2·6 to 5 units, trypsin 6 to 46 units; i.e., both enzymes were within the normal range.

Fat Absorption Studies in Pancreatic Fibrosis and Coeliac Disease. The mean percentage fat absorption in each of the 14 children with pancreatic fibrosis who had a fat balance before pancreatin therapy is shown in Table 1, from which it may be seen that 11 had figures below 60%. As the three patients with pancreatic fibrosis whose fat absorption figures were over 60% were all under 1 year of age, it seemed possible that of patients with this disease infants who receive a predominance of milk in their diet might have greater fat absorption figures than older children receiving a mixed diet. In Table 2 and Fig. 1, where we have compared the fat balance findings in pancreatic fibrosis and coeliac disease, we have divided the children in each group

TABLE 1
PANCREATIC ENZYMES AND FAT ABSORPTION IN PANCREATIC FIBROSIS

Patient	Age	Duodenal Enzymes		Fat Absorption (%) (Mean of 5 to 10-Day Balance)
		Lipase (units/0·1 ml.)	Trypsin (units/1 ml.)	
1	2 wk.	0·3	0	Not done
2	6 wk.	0	0	" "
3	8 wk.	0	0	" "
4	(*a*) 10 wk.	0·3	1·5	"
	(*b*) 11 mth.	0	0	79·5
5	2 mth.	0	0	Not done
6	3 mth.	0	0	40
7	2 mth	0	0	48
8	5 mth.	0	0	72
9	7 mth.	0	0	81
10	(*a*) 9 mth.	0·1	0	Not done
	(*b*) 2½ yr.	0·1	0	39
11	9 mth.	0	0	58
12	(*a*) 9 mth.	0	0	54
	(*b*) 1½ yr.	Not done	Not done	57
13	1½ yr.	0	0	54
14	(*a*) 2 yr.	0·3	7·8	Not done
	(*b*) 3 yr.	0·1	0	26
15	2 yr.	0	0	52
16	3½ yr.	0·1	0	52
17	4 yr.	0	0	52

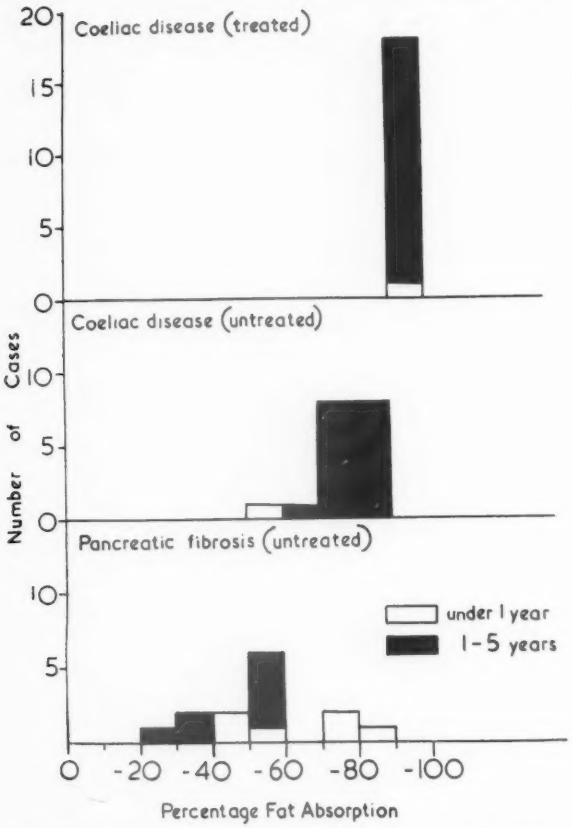

FIG. 1.—Fat absorption in pancreatic fibrosis and coeliac disease.

into those under and those over 1 year of age. Before treatment with a wheat gluten-free diet only one of the 18 children with coeliac disease had a fat absorption below 60%. She was 11 months old, the only child in this group who was under 1 year of age; the marked steatorrhoea in her case may have resulted in an unusually early diagnosis of coeliac disease. After treatment with a wheat gluten-free diet the fat absorption figures in all 18 children had risen above 90% (mean 92·5). It would thus appear that in children over 1 year of age steatorrhoea is more marked in pancreatic fibrosis than in coeliac disease but that in children under 1 year of age, with pancreatic fibrosis, fat absorption may be relatively high.

Systemic Hyperlipaemia. The maximum chylomicrograph increments obtained after a standard fat meal in the three groups are shown in Table 3. Of the 22 children with pancreatic fibrosis, 21 had a maximum chylomicron increment under 50 and in 18 the maximum increment was below 25. On the other hand, of the 18 children with untreated coeliac disease, only three had a maximum increment below 50. That the chylomicograph is frequently depressed, however, in untreated coeliac disease (as previously shown by Anderson *et al.*, 1952) is evident from the finding that only four of these patients had a maximum increment over 150 compared with 10 of these children after treatment. It was interesting that the only case of pancreatic fibrosis with a maximum increment over 50 was an infant 10 weeks of age in whom duodenal intubation had shown the presence of trypsin and lipase, although both greatly reduced below normal values. On reinvestigation when 11 months old he then had complete absence of duodenal enzymes and a flat chylomicrograph. It thus appears that although a flat chylomicrograph (maximum increment below 50)

TABLE 2

FAT ABSORPTION IN PANCREATIC FIBROSIS AND COELIAC DISEASE

	Total Patients	Percentage Fat Absorption							
		20–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
Pancreatic Fibrosis									
Under 1 yr.	6	–	–	2	1	–	2	1	–
1–5 yr.	8	1	2	–	5	–	–	–	–
Totals	14	1	2	2	6	–	2	1	–
Coeliac Disease (untreated)									
Under 1 yr.	1	–	–	–	1	–	–	–	–
1–5 yr.	17	–	–	–	–	1	8	8	–
Totals	18	–	–	–	1	1	8	8	–
Coeliac Disease (treated)									
Under 1 yr.	1	–	–	–	–	–	–	–	1
1–5 yr.	17	–	–	–	–	–	–	–	17
Totals	18	–	–	–	–	–	–	–	18

TABLE 3

CHYLOMICROGRAPHS IN PANCREATIC FIBROSIS AND COELIAC DISEASE

	Total Cases	Number of Cases with Maximum Increment						
		0–25	26–50	51–75	76–100	101–125	126–150	150+
Pancreatic fibrosis ..	22	18	3	–	–	–	–	1
Coeliac disease (*a*) untreated ..	18	1	2	6	3	–	2	4
Coeliac disease (*b*) treated	18	–	–	1	2	3	2	10

TABLE 4

EFFECT OF PANCREATIN ON FAT ABSORPTION

Patient	Age (yr.)	Daily Fat Intake (g.)	Percentage Fat Absorption			Dose of Pancreatin for Optimal Fat Absorption (g. B.P.)
			Without Pancreatin	Optimal Attained on Pancreatin	Increase on Pancreatin	
A	2/12	20	48	77	29	1·0 S*
B	8/12	40	54	86	32	1·0 S
C	1	30	79·5	74	nil	
D	1½	40	54	79	25	1·5 S
E	1½	40	57	73	16	1·0 T
F	2	40	52	63·5	11·5	2·0 S
G	2½	42	39	76	37	2·0 T
H	2½	40	58	82	24	1·0 T
I	4	40	52	74	22	3·0 T
J	4	40	32	55	23	2·0 S
K	5	50	26	62	36	2·0 T
Mean			50	72·8	23·2	

* S='single' strength. T='triple' strength.

TABLE 5

CHYLOMICROGRAPHS IN PANCREATIC FIBROSIS AFTER FEEDS OF SIMILAR FAT CONTENT WITHOUT PANCREATIN AND WITH PANCREATIN

Patient	Age	Chylomicrograph Maximum Increment	
		Without Pancreatin	With Pancreatin
A	6 mth.	0	118
B	1½ yr.	16	200
C	2½ yr.	12	173
D	2 yr.	1	114
Mean		7	151

is a very useful test of pancreatic fibrosis, yet the chylomicrograph may be normal when the pancreatic pathological process has not yet resulted in complete absence of lipase.

Effect of Pancreatin on Fat Absorption by Fat-Balance Studies. From Table 4 it will be seen that pancreatin resulted in considerable improvement in fat absorption in 10 out of 11 children with pancreatic fibrosis. The percentage increase in fat absorption ranged from 11 to 29 with a mean of 23·2%. It was found that for each patient a certain dosage of pancreatin produced optimal fat absorption, and that an increase above this dosage produced no further improvement and sometimes even deterioration. The amount per feed required for optimal fat absorption ranged from 1 g. B.P. 'single' to 3 g. B.P. 'triple'. This dosage bore no obvious correlation to the daily fat intake or to the percentage fat absorption before pancreatin was given. It will be noted, however, that the child with the highest fat absorption before treatment was the one who showed no improvement with pancreatin. Although the number of cases in this study was small, a rough correlation was found between the optimal dosage of pancreatin and the age of the child.

Systemic Hyperlipaemia after Pancreatin. The maximum chylomicron increments obtained in four children with pancreatic fibrosis after feeds of similar fat content (*a*) without pancreatin and (*b*) with pancreatin are shown in Table 5. In each case the chylomicrograph obtained after the feed with pancreatin was considerably higher than that without pancreatin.

Discussion

The differential diagnosis between pancreatic fibrosis and coeliac disease is frequently difficult. Although absence or marked reduction of pancreatic enzymes in duodenal juice is undoubtedly the most reliable diagnostic test of pancreatic fibrosis, duodenal intubation is not always possible either because the child may be too ill or because of lack of radiological screening facilities. A low content of proteolytic activity in the stool is sometimes used as a diagnostic test of pancreatic insufficiency, but Sammons, Ross and Wood (1954) have shown that this is an unreliable index of pancreatic function. Our present studies have demonstrated that both fat-balance studies and chylomicrographs may be of considerable value in the differential diagnosis of pancreatic fibrosis and coeliac disease. Fat-balance studies revealed a clear-cut difference in the fat absorption figures between the two conditions in children over 1 year of age; in children under 1 year of age receiving a predominance of milk in their diet this difference was not observed. A maximum chylomicron increment below 50 was strongly in favour of pancreatic fibrosis; this finding is in keeping with those reported by Elghammer, Reichert and Philipsborn (1950) and Payne (1952). Moreover, we found that the chylomicrograph was generally more useful than a fat balance in the differential diagnosis as it is simple to carry out and is less time consuming and troublesome for patient, laboratory staff and nursing staff. Again, since pancreatic fibrosis is a hereditary disease, it is sometimes desirable to exclude its presence in siblings and for this purpose the chylomicrograph is a useful out-patient test.

We have demonstrated the value of pancreatin in improving fat absorption as evidenced both by fat-balance studies and by chylomicrographs. For each child there was a certain dosage of pancreatin which produced an optimal increase in percentage fat absorption; this was always accompanied by a progressive increase in weight. Increase in this dosage not only failed to produce further improvement in fat absorption but frequently resulted in deterioration. The reason for this is unknown but it may be that for optimal fat absorption lipolysis must be such as to produce a certain proportion of neutral fats and fatty acids. It was of interest that, although there was considerable improvement in fat absorption with pancreatin, in all the children the highest figures were considerably below normal. Several hypotheses may be advanced to explain this. It may be that pancreatin even when given with the meal achieves less intimate mixture with the food than does the coordinated flow of pancreatic juice. Again, the lipase/trypsin ratio may be of importance: in pancreatic extracts this ratio is much lower than that found in duodenal juice. It also seems possible that besides lipase some other factor which is necessary for normal fat absorption may be absent or depressed in the child with pancreatic fibrosis.

It is obvious that for assessment of pancreatic therapy fat-balance studies cannot be carried out on all children with pancreatic fibrosis. Again, the increase obtained in the chylomicron increment after a standard fat meal with pancreatin is not a satisfactory index of the dosage required, as we found that the optimal dosage for any child as assessed by fat-balance studies did not always correspond to the dosage which gave the highest increase in chylomicron increment. Although the number of cases studied in the present series was

small, a rough correlation was however obtained between dosage of pancreatin required for optimal fat absorption and the age of the child. For the pancreatin preparation used in the present study the approximate dosage required in relation to age was as follows: under 1 year, 1 g. B.P. 'single'; 1-2 years, 2 g. B.P. 'single'-1 g. B.P. 'triple'; 2-5 years, 1 g. B.P. 'triple'-3 g. B.P. 'triple'. Since these studies were done we have found that pancreatin U.S.P. is considerably more potent, weight for weight, than pancreatin B.P. (0·5 g. U.S.P. 'single' strength powder contained 15 units lipase and 30 units trypsin), although the highest fat absorption attained in any one child with either type was approximately the same. In children over 2 years of age, where it is sometimes desirable to reduce the bulk of the powder given with each meal in order to disguise its taste, U.S.P. pancreatin may be preferable to B.P.

At the time of the present report it was not possible to deduce from our studies if pancreatin therapy had had any influence on the prevention or amelioration of respiratory involvement, for not only had the follow-up period been too short for this purpose but there were insufficient children in the series to analyse in separate age groups. It was of interest, however, that of the six infants under 1 year of age who had fat-balance studies before being given pancreatin, three had fat absorption figures over 60%, and two of these died of acute respiratory infections before the age of 1 year, whereas of the three babies with a low fat absorption (below 60%), one died. These findings do not support the idea that those with a gross defect in fat absorption are most liable to pulmonary infection; this aspect of the problem, however, requires further study.

Summary

The fat absorption defect was investigated by means of fat-balance studies and chylomicrographs in a series of 22 children under 5 years of age who were suffering from pancreatic fibrosis, and the findings compared with those found in a series of 18 children under 5 years of age with coeliac disease.

Fat-balance studies showed that in the children over 1 year of age the fat absorption percentages in those with pancreatic fibrosis, before pancreatin therapy, were all under 60, whereas in the children with coeliac disease the figures were over 60% even when the condition was active. In the children under 1 year of age receiving a predominance of milk in their diets, this difference in fat absorption between pancreatic fibrosis and coeliac disease was not observed.

The chylomicrograph was a very useful test in differential diagnosis: a maximum chylomicron increment of under 50 particles was obtained in 21 out of 22 children with pancreatic fibrosis but in only three out of 18 children with active coeliac disease.

The administration of pancreatin with feeds resulted in considerable improvement in fat absorption in 10 out of 11 children with pancreatic fibrosis, the mean increase in fat absorption being 23·2%. It was found that for each patient there was a certain dosage of pancreatin which gave optimal fat absorption as assessed by fat-balance studies, and that this dosage bore a rough correlation to the age of the patient.

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OBSERVATIONS ON WEIGHT GAIN IN INFANTS

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There is general acceptance that weight gain in infants is a sensitive measure of health and on this account, both in welfare clinic practice and in the private practice of paediatrics, it is usual to keep a record of infants' weights. This record is compared with a table of mean values which is commonly presented as a graph covering the first year. The origin of these graphs is seldom if ever disclosed and reference to current paediatric literature is singularly uninformative on present-day weight standards of British infants. For this reason, and because it has already been shown (Thomson, 1954) that the mean weight of 6-month-old infants has increased appreciably when compared with the mean weight of infants of over 30 years ago, an enquiry into weight gain in infants at the present time was felt to be justified.

Method

In general, enquiries of this nature take one of two forms; they may be longitudinal or latitudinal. In the former method the same infants are observed at predetermined ages throughout the year. This method is difficult to carry out, and while it has the merit of always making observations of the same infant, this very merit is subject to the objection that observations made at one age may merely be projected to influence observations made at a later age. An example of this influence is demonstrated in Fig. 1 which shows how the mean birth weight of various groups of infants determines the mean weight of the group at the end of a year. This is no new observation; it was made by Camerer (1893) and recently repeated by Parfit (1951).

In the present enquiry a longitudinal approach was attempted, but the wastage of observations was so great that the method was abandoned and a latitudinal approach adopted.

In this method the infant population of one clinic were sampled at predetermined age periods throughout the year. The sampling ages decided upon were: 2 weeks ± 2 days; 4, 8, 12, 16, 20 and 24 weeks all ± 3 days; 28, 32 and 36 weeks all ± 5 days and 40, 44, 48 and 52 weeks all ± 7 days. The effect of allowing a greater range of age with increasing age of the infant is negligible; for example, the 52 weeks ± 7 days male group has a mean age of 51 weeks 6·42 days with a standard deviation of 3·54 days; moreover, as will be shown later, variation of weight gain diminishes with increasing age. Further, as the trend is for more and more mothers to cease attending the clinic as the infant grows older, the

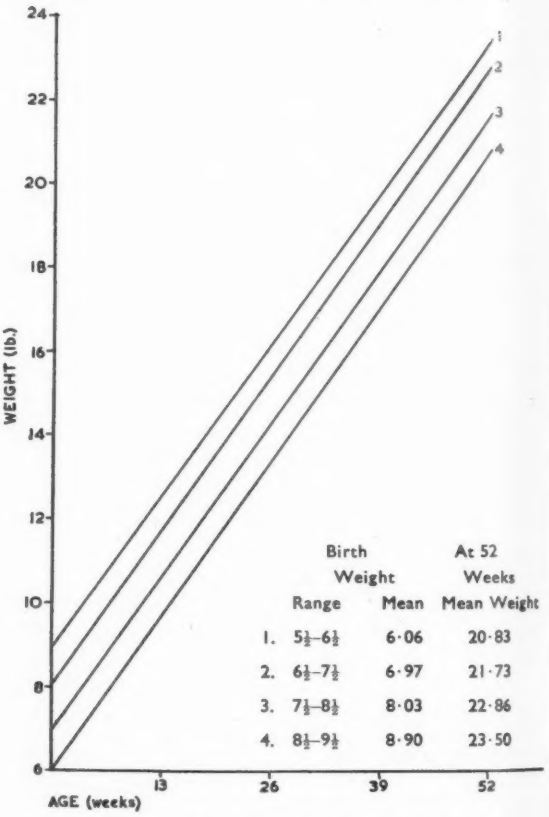

FIG. 1.—Mean weight at 52 weeks related to birth weight.

TABLE 1

MEAN BIRTH WEIGHTS AND WEIGHT GAIN OF MALE AND FEMALE SINGLETON INFANTS OF FIRST PREGNANCIES

Age (wk.)	Number		Birth Weight (oz.)				Weight Gain (oz.)			
			Male		Female		Male		Female	
	M.	F.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
2	106	109	119·37	14·96	114·79	14·51	1·53	7·29	1·58	6·76
4	190	196	118·6	15·42	115·7	15·06	17·29	10·49	15·88	9·75
8	182	168	117·7	14·84	116·33	14·42	49·37	17·12	44·78	14·65
12	150	147	117·6	15·52	116·34	14·22	81·04	18·83	70·675	19·73
16	146	121	117·0	13·82	115·56	14·29	104·82	21·74	95·45	22·79
20	142	118	117·65	13·69	116·9	14·79	126·1	24·5	114·78	25·53
24	137	127	117·93	14·01	115·5	14·4	147·39	25·4	134·4	26·55
28	126	113	116·45	13·81	115·12	14·84	168·10	28·73	153·02	29·46
32	126	115	115·5	13·1	116·13	14·74	184·86	29·33	167·9	30·87
36	110	102	115·55	13·72	115·35	14·03	197·9	27·41	182·5	33·2
40	140	124	117·03	13·75	117·2	13·96	210·68	28·53	192·68	33·67
44	125	121	116·5	13·68	118·37	14·375	224·48	31·45	205·26	36·24
48	146	114	117·07	13·06	118·0	14·14	237·65	36·24	217·4	37·82
52	111	130	117·01	12·43	117·5	15·55	246·3	36·4	224·3	34·19

greater age range towards the end of the year permits of a more rapid accumulation of data than would otherwise be possible.

Source of Material

The observations were made on infants who were born in the Simpson Memorial Maternity Pavilion of the Royal Infirmary, Edinburgh, and an accurate record of birth weight is available. They attended the infant welfare clinic in the same hospital. In an effort to exclude the prematurely and postmaturely born, the enquiry was confined to infants within a birth weight range of over 5½ lb. to 9½ lb. Only singleton legitimate infants were considered. Further, because the mean birth weight of first-born infants is less than the mean birth weight of subsequent infants (McKeown and Gibson, 1951) only infants resulting from first pregnancies are dealt with. The naked infants were weighed on a beam-balance by pupil-midwives who were supervised by me. The infants were drawn from social classes III, IV and V. In each sex age group there were more than 100 observations.

Results

The weights were taken to the last complete ounce and from the data obtained the mean birth weights and the mean weight gains with their respective standard deviations for each sex at each age period were calculated (Table 1, Fig. 2).

Discussion

Influence of Sex. It has long been recognized that the pattern of mean weight gain is influenced by sex and that throughout the first year the male mean weight gain is greater than the female (Faber, 1920; Höjer, 1925; Hill and Magee, 1938; Lewis-Faning and Milligan, 1944; Schiötz and Berghoff, 1928; Norval, Kennedy and Berkson, 1951; Parfit, 1951). The present investigation confirms that this occurs when the observations are restricted to full-time singleton infants of first pregnancies and disagrees with the contrary findings of Bayley and Davis (1935). The extent of the difference between the sexes may be gauged by noting that the male mean weight gain at 26 weeks, 157·6 oz., is not attained by the female until three weeks later, and that the female mean weight gain at 52 weeks, 224·3 oz., has already been attained by the male eight weeks previously. Thus, there is justification for the separate recording and assessment of male and female gains.

Despite the differing patterns of weight gain by the sexes, they possess two things in common. First, one-quarter, one-half and three-quarters of the mean weight gain for the year in both sexes is achieved at the same age, namely, 10 weeks, 19-20 weeks and 32 weeks. A similar deduction can be drawn from the data presented by Parfit (1951). The approximation is not so close when the data of Norval *et al.* (1951) are considered. This may be explained by the different composition of the group of infants on the one hand and the relation of their observations to insufficiently precise age points on the other. The second point of similarity concerns the variability of the weight gain. This declines with increasing age (Fig. 3). (Variability is measured by stating the standard deviation as a percentage of the mean and calling it the coefficient of variation.)

Correlation of Birth Weight and Weight Gain. The correlation coefficients between the observed birth weights and weight gains were calculated and are

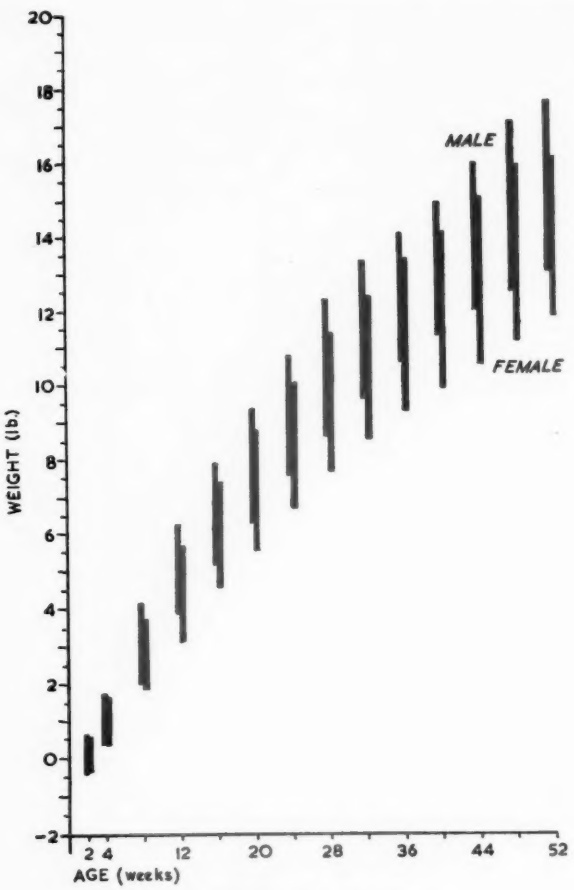

FIG. 2.—Weight gain in the first year.

shown graphically in Fig. 4. They display one distinctive feature in that with two exceptions they are negative in character. This suggests that in all age groups, in both sexes, infants of great birth weight gain less than infants of low birth weight. Some confirmation of this may be obtained from inspection of Fig. 1 which illustrates a slight convergence of the lines of weight for infants of the high and low mean birth weight groups. This observation on full-time singleton legitimate infants confirms the similar observation made by Norval *et al.* (1951) and by Parfit (1951); it also has the support of Herdan (1954). At the same time, it must be pointed out that from the age of 4 weeks onwards in males and 20 weeks onwards in females, the correlation coefficients which have been obtained are not significant. As for the observations which are significant—there are two male and six female ones—the degree of association found is low. That this degree of association, though statistically significant, is of doubtful validity is shown by a consideration of part of a separate, as yet unpublished study, concerned with infant weight gain in breast- and bottle-fed infants. Included in this study are 40 pairs of healthy first-born singleton female infants, the pairs being matched to the same ounce of birth weight. One of each pair was wholly bottle fed and the other wholly breast fed. At 16 weeks before mixed feeding was begun the weight gain was assessed. The resulting data are presented in Table 2. These show that, while the mean weight gain with standard deviation of the breast- and bottle-fed groups are similar and approximate to the same data for 16-week-old female infants in Table 1, the correlation coefficients between birth weight and weight increment are of no statistical significance. This is so whether the two groups are considered separately or jointly. In general, then, the present investigation suggests very strongly that there is no true association between birth weight and post-natal weight gain. In this conclusion one is supported by the observations of Norval *et al.* (1951) and Parfit (1951). The support given by Herdan (1954) is slightly qualified, but this qualification may well be occasioned by the inclusion of prematurely and postmaturely born infants in his investigation and the absence of differentiation between the sexes.

The absence of an association between birth weight and postnatal weight gain has a practical application, since it follows that, if we desire to compare the progress of different infants with each other, it is truly the progress, that is, the post-natal weight gains, which we must compare and not progress plus birth weights. Further, if a common measuring rod of such progress is to be used it must be derived from records of post-natal weight gain as has been done in Table 1 and Fig. 2. In short,

TABLE 2
WEIGHT GAIN IN 40 MATCHED PAIRS OF FEMALE SINGLETON FIRSTBORN INFANTS

Number	Birth Weight (oz.)		Weight Gain (oz.) at 16 weeks		Coefficient of Correlation
	Mean	S.D.	Mean	S.D.	
40 (breast fed)	111·375	13·80	96·75	22·78	−0·23
40 (bottle fed)	,,	,,	96·48	20·65	−0·01
Combined groups	,,	,,	96·61	21·73	−0·11

it is recommended that where clinics use a graphical method of recording progress, the universally used method of recording infant weight should be abandoned and the graph begun at zero on the birthday so that only gains and losses of weight are recorded thereafter.

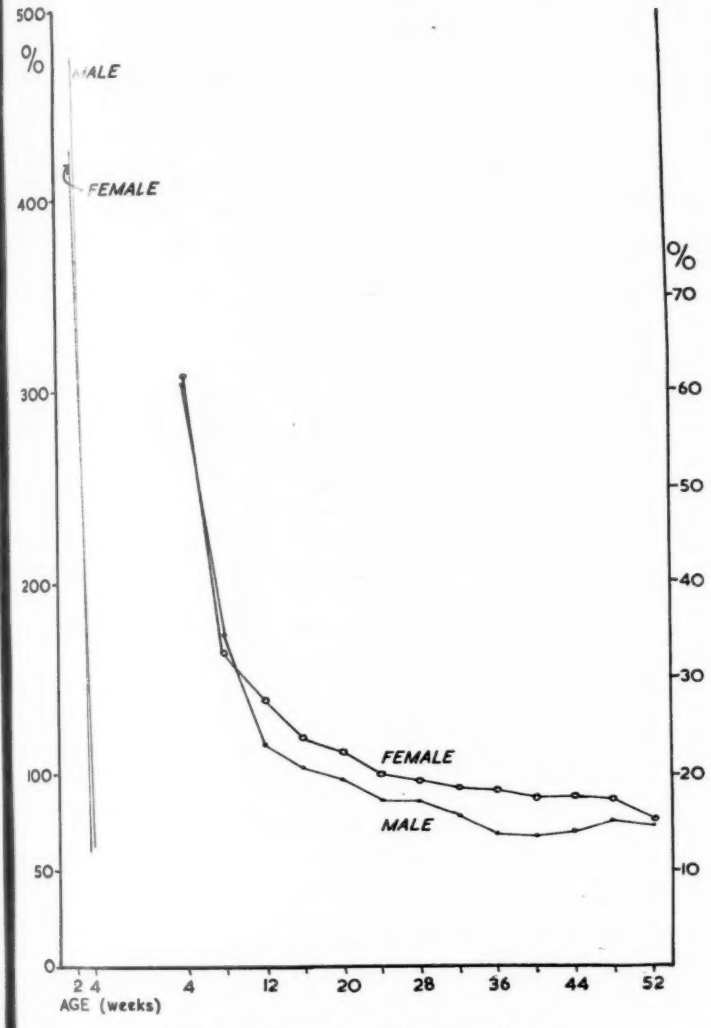

FIG. 3.—Coefficient of variation of weight gain.

The idea that birth weight controls post-natal weight is of long standing and the statement that an infant doubles the birth weight by 5 months of age and trebles it at a year is to be heard in both lay and paediatric circles. Such statements are also to be found in paediatric literature and may be read in standard paediatric textbooks. Were such a statement true, the correlation coefficients would have been uniformly positive. The lines of weight shown in Fig. 1 would have diverged and not converged while the coefficient of variation of weight gain would have remained much the same throughout the year.

In the course of human growth through infancy and childhood there is a progressive diminution of the coefficient of variation of weight gain. This is a biological phenomenon and is in harmony with the absence of a relationship between birth weight and postnatal gain.

We may well ask, What is the origin of the statement? It is probably due to a failure to appreciate one of the fundamental characteristics of the statistical approach, namely, that a 'population' of observations may acquire characteristics which are not possessed by the individual observations which make up that population. In the case of infant weight in the present investigation, if sex differentiation is discarded, it can be seen from Table 1 that the mean weight at 52 weeks is approximately three times the mean birth weight. That, however, is quite different from saying that the individuals in the 52-week group are individually three times their respective birth weights. It can also be pointed out that sex influence alone is enough to disprove the statement, since in the

TABLE 3

MEAN WEIGHT GAINS AT 52 WEEKS COMPARED

	Mean Birth Weight (oz.)		Mean Weight Gain (oz.)			
			11-12 Months		52 Weeks	
	Males	Females	Males	Females	Males	Females
Norval *et al.* (1951)	121·6	116·8	236·8	216·0		
Parfit (1951)	122·3	118·3			247·6	226·3
Present investigation	117·01	117·5			246·3	224·3

52-week group of the present enquiry no difference is shown between the mean birth weights of males and females, but a difference of 22 oz. is shown between the means of the 52-week weight gains.

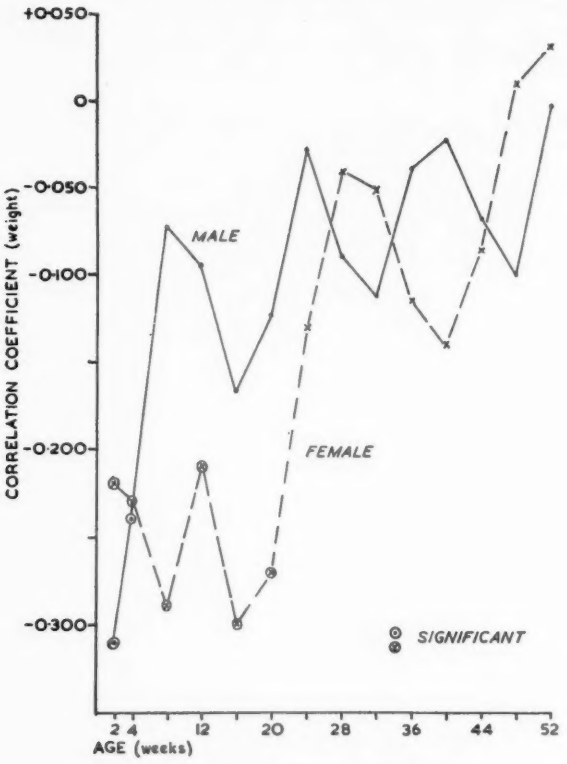

FIG. 4.—Birth weight and weight gain correlation.

The Amount of the Weight Gain. It is a matter of some importance and interest to compare the mean weight gain in the present enquiry with the mean weight gains reported by other observers. There are, however, no publications which deal exclusively with singleton legitimate infants born of first pregnancies and differentiated by sex. With this reservation in mind the publications of Norval *et al.* (1951) and Parfit (1951) may be considered. Reference to Table 3 shows that the mean weight gain at 52 weeks reported in the present enquiry approximates closely to the mean weight gains calculated from the data in the aforementioned publications. It is possible to select from Parfit's publication data referable to the same birth weight range as that of the present investigation and this has been done in Table 3.

Such close approximations suggest that the mean weight gains disclosed by the present investigation are reasonable and reliable. In view, therefore, of the very considerable social changes which have taken place during the first half of the century it is of great interest to compare the mean weight gains of the present enquiry with the weight gains of a generation ago.

Although it is ever to be regretted that in their comprehensive enquiry into heights and weights of infants and children, Paton and Findlay (1926) did not include information concerning birth weight, their publication does serve as a basis for comparison if one will accept mean total weight for that purpose (Table 4). Because of the increase in weight of 52-week-old infants shown in Table 4 the following condensation from Paton and Findlay is worth noting:

> 'The study was made upon the populations of the slums of the three Scottish towns—Glasgow, Edinburgh and Dundee . . ., but the danger of concentrating on families living in the worst conditions was guarded against and largely obviated by the random selection of families through the child welfare centres. The mothers attending the centres in Glasgow and Dundee were of a poorer class than those attending the two centres in Edinburgh at which records were made. These two centres were attended largely by a superior working class and in the case of one of the centres by large numbers of the wives of artisans in addition to those of labourers. In Edinburgh the centres were preventative rather than curative so that a greater proportion of the babies were in a good state of health; the amount of

TABLE 4
CONTRAST OF INFANTS' MEAN BODY WEIGHT

Author	Mean Body Weight (oz.) at 3 Months		Mean Body Weight (oz.) at 6 Months		Mean Body Weight (oz.) at 9 Months		Mean Body Weight (oz.) at 12 Months	
	Male	Female	Male	Female	Male	Female	Male	Female
Paton and Findlay								
Glasgow	179·0	169·0	239·0	219·0	276·5	256·0	312·0	285·0
Dundee	187·0	171·5	240·5	227·0	281·0	264·0	293·0	279·0
Edinburgh	178·0	157·0	228·0	215·5	273·0	263·0	317·0	303·0
Present Inquiry								
Edinburgh	198·6	187·0	276·0	256·0	327·7	309·9	363·3	341·8
Parfit								
Oxford	209·4	194·6	273·2	260·9	331·5	306·4	369·9	344·6

free milk distributed at the two centres in Edinburgh was practically negligible.'

The difference between the weights recorded by Paton and Findlay and those now recorded are eloquent testimony to the vast improvement which has occurred in the welfare of infants.

In view of this change it was thought worth comparing the mean weight gains now reported with the expected mean weight gain shown on the graph record used in infant welfare clinics. For this purpose a copy of the infant welfare weight graph record was obtained from four local authorities. The expected mean weight gain shown upon them was calculated by deducting the given mean birth weight from the given 52 weeks' mean weight. Since these graphs do not differentiate between the sexes, in order to make a comparison the mean weight gain of the present enquiry was calculated without differentiation for sex (Table 5).

TABLE 5

RESULTS OF PRESENT-DAY PRO-FORMA INFANT CLINIC WEIGHT CHARTS COMPARED WITH PRESENT INVESTIGATION

Local Authority	Mean Birth Weight (oz.)	Mean Weight at 52 Weeks (oz.)	Weight Gain (oz.)
Number 1 ..	112·0	317·0	205·0
„ 2 ..	112·0	317·0	205·0
„ 3 ..	116·0	320·0	204·0
„ 4 ..	120·0	340·0	220·0
Present investigation ..	117·3	351·7	234·4

From mere inspection of the cards of local authorities numbers 1 and 2, it is plain that the card in use is a copy of a record which appears in Paton and Findlay (1926), Appendix 1. It is part of a 'schedule which was prepared for the carrying out of the investigation in child welfare centres' and is not the result of Paton and Findlay's investigation.

Local authority number 3 is Edinburgh and the record in use today was prepared by the late Dr. T. Y. Finlay as a result of his own investigation (Finlay, 1924) when between 1919 and 1923 he collaborated with Paton and Findlay. It is a valid comparison with the results now reported from the same city. Such comparison shows that the mean weight at 52 weeks, undifferentiated for sex, is today 30 oz. greater.

In the case of authority number 4 the expected weight gain at 52 weeks, though below that shown in the present investigation, is 1 lb. greater than that expected by local authorities numbers 1, 2 and 3. The lay-out of the card of local authority number 4 is superior and may well be of recent origin for on it provision is made for recording tuberculin skin tests and vaccination by B.C.G. From these observations it may be said that the weight progress of the vast majority of infants in Scotland who attend infant welfare clinics is recorded on cards which are outmoded.

Summary

From 1,737 observations on males and 1,605 observations on females, the weight gain at four-weekly intervals during the first year of life has been calculated. The observations were made on legitimate, singleton, first pregnancy infants whose birth weights were within the range of over 5½ lb. to 9½ lb.

Sex exerts an influence upon the pattern of weight gain.

Apart from a doubtful and slight relationship in the early weeks of life, the correlation coefficients between birth weight and postnatal weight gain were not of statistical significance. They were almost uniformly negative.

The prevalent idea that birth weight is doubled and trebled at certain ages is examined and shown to be untenable.

Evidence is offered to show that there is a strong tendency for infants of lesser birth weight to gain weight more rapidly than infants of greater birth weight.

It is suggested that the customary method of recording infant weight should be abandoned and only gains and losses recorded from birth.

From a comparison of the infant weights reported by Paton and Findlay (1926) with those of the present investigation, an increase in the mean body weight of male and female infants of the order of 2 lb. is found. It is suggested that the graph weight cards in use in local authority infant welfare clinics are largely outmoded.

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AN ANTHROPOMETRIC STUDY OF EDINBURGH SCHOOLCHILDREN

PART I. METHODS, DATA AND ASSESSMENT OF MATURITY

BY

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The present study represents one part of a joint investigation of a stratified sample of Edinburgh schoolchildren carried out in collaboration with J. N. Mansbridge (who was investigating dentition and dental caries in the same sample) and with the statistical help of Dr. L. Stein and staff of the Department of Social Medicine, University of Edinburgh. The purpose of the anthropometric study was to provide, in the first instance, cross-sectional data which could be used for comparison with similar measurements on other groups of Edinburgh children (e.g., premature babies, mental defectives and others), for comparing children in this city with other geographical populations and for subsequent use in studies of secular changes in the growth of schoolchildren over a period of years. The lack of recent Scottish data for any measurements other than those of height and weight, and the incompleteness even of such data over the whole age-range 5 to 18 years, was an additional reason for undertaking the survey. Clinical assessment of maturity was included in the investigation in order to provide data on age-onset of puberty in both sexes, for which no recent Scottish figures are available. The methods of sampling, techniques of measurement and statistical treatment are outlined, and the basis of classification of the children into maturity groups is indicated. All maturity-grading and measurements, except where otherwise stated, were carried out by one of us (H.S.P.). The basic data which are now presented will be discussed more fully, together with the frequency distributions of length and weight in a subsequent paper (Part II).

Methods

Sample. It was desired to obtain as good a sample as possible of the day pupils in the city between the ages of 5 and 18 years; the planning and stratification of the sample was undertaken by the statistical section of the Department of Social Medicine. Ages were reckoned from the date of birth to the date of examination. Since socio-economic factors often influence growth, the children were divided into two groups; those attending local authority schools (non-fee-paying) and those attending private schools (fee-paying). The children were placed in age groups and the proportions of non-fee-paying and fee-paying were dictated by the proportion of schoolchildren in the appropriate group being educated in those types of school in Edinburgh during 1951. The percentages of boys from fee-paying schools in the investigation in each year-age group were approximately 13 from 5 to 11 years, 15 from 11 to 14 years, 18 from 14 to 15 years, and 44, 52 and 56 at 15+, 16+ and 17+ years respectively. The corresponding figures for girls were approximately 12% from 5 to 11 years, 14% at 11 to 13 years, 12% at 13 to 15 years, and 31, 43 and 44% at 15+, 16+ and 17+ years respectively. The research was made on 1,730 pupils, there being rather more boys than girls. The data for the two sexes were recorded separately.

It was decided to select a few schools with large numbers of pupils extending over a wide age range to save unnecessary disruption of educational programmes, time and labour. Practical considerations prevented undertaking a theoretically more scientific approach. The subjects were drawn from nine schools; five were local authority and four fee-paying. The city School Medical Officer initially chose two primary (mixed) and two secondary (mixed) schools, care being taken to exclude those of a special character, e.g., of a religious persuasion. The schools were divided into age groups and the required sample taken by random number. Sufficient numbers of non-fee-paying subjects in the 5–14-year-old age groups were obtained in this way and the sample was entirely random. Another secondary school was later required to make up the children in the 15–17-year-old age groups to an adequate number. Selection in this school was also initially by random number, but the sample is biassed, particularly in the 16–17-year-old age groups, as, owing to the small numbers available, little selection was possible and most or all had to be included.

The fee-paying schools included two boys' schools and two girls' schools. The fees in all were substantial.

There were so few schools which fulfilled the criteria laid down that those which were able to cooperate in the investigation were used. Owing to the small numbers of fee-paying pupils required in the 5–14-year-old age groups individuals to be measured were not chosen at random, but by taking every third child in the age group series. The same general procedure was adopted for the older age groups, but shortages in the numbers available often made any selection procedure impracticable.

The great majority of the measurements were made during the autumn and spring terms 1951–52, but owing to difficulties in obtaining adequate samples of the older age groups, the investigation was not completed until 1953.

Measurement. Nine body measurements were taken on each child. They consisted of recumbent supine length, i.e., crown-heel length, crown-rump length (stem-length), and span; bi-acromial diameter and intraspinous pelvic width; weight; and the circumference, length and breadth of the head.

THE LINEAR BODY MEASUREMENTS. These were the first three listed above. The children wore vest and pants, knickers or shorts. Most of the readings were taken by H.S.P. and the remainder by J. N. Mansbridge.

RECUMBENT CROWN-HEEL LENGTH. This was measured by means of a simple apparatus consisting of a broad 6½-ft. wooden base with a fixed vertical board at one end and a sliding vertical board at the other which moved up a central slot. A scale graduated in feet and inches was inlaid. The accuracy of the scale was checked. The apparatus was made portable by hinging it in the middle of its length. The child lay down supine and straight in the machine. The head in the standard position (i.e., with the Frankfort plane vertical and the bi-auricular plane horizontal) was rested firmly against the fixed head-piece; the feet were placed together and dorsiflexed and the sliding board pushed up against the two heels after which the soles were allowed to fall comfortably into position against the vertical foot-piece which was screwed down. Readings were taken to the nearest one-eighth of an inch. It was found in practice that the commonest errors in position which had to be avoided were: the head not being firmly in position against the board, the head being moved to one side, or the neck being flexed excessively. Much more rarely the child did not lie straight.

CROWN-RUMP (STEM) LENGTH. This was also measured by the apparatus described. The position taken up by the child was similar to that for recumbent length. The legs were then flexed so that the thighs were at right angles to the trunk with the knees flexed. The sliding board was moved up and pressed firmly against the buttocks and the distance between the ischial tuberosities and the vertex of the head noted in the same way as for crown-heel length.

SPAN. The same apparatus was used to measure the span. This was recorded as the distance between the tips of the middle fingers of each hand with the arms abducted at a right angle to the body. The child lay down on the back with the body and arms in the general position indicated in such a way that the span came to lie centrally along the measuring board. The forearms were fully pronated with palm downwards and fingers together and in the extended position. The measurement was recorded to the nearest one-eighth of an inch.

MEASUREMENT OF BODY MASS: WEIGHT. All weighing machines were checked for accuracy before use. In the local authority schools modern lever type machines manufactured by Avery were provided. Weights were recorded to the nearest ¼ lb. The private schools varied. One boys' school and one girls' school had lever balances of an older type, recording weights to the nearest ¼ lb. The other two schools had no weighing machine. A portable 'waymaster' spring balance was used and errors from the true weight corrected. Recording of data to the nearest pound was the greatest accuracy obtainable in these schools. The nude weights of the children are given. The younger children were weighed without clothes. Those who were maturing sexually were given a surgical gown to cover themselves and the weight of the gown substracted from the recorded weight. The great majority of the readings on the Avery machines were taken by J. N. Mansbridge and those on the 'waymaster' by H.S.P.

MEASUREMENTS OF BODY WIDTH. Two were taken, i.e., bi-acromial diameter and intraspinous pelvic width. A Collin's pelvimeter was used and data recorded to the nearest half centimetre.

Bi-acromial Diameter. The child removed the vest unless it was of such a type that the acromial processes were exposed and palpable. The standing position was adopted with the arms by the side, care being taken that the shoulders were neither raised nor projected anteriorly. The examiner stood behind the subject. Holding the pelvimeter parallel with the ground, the tips of the blades were pressed firmly downwards and medially against the acromion processes. In practice a definite niche between the head of the humerus and acromial process of the scapula was found.

Pelvic Width. The child assumed the erect position with the feet together. The examiner stood in front, and having exposed the hips, laid the points of the pelvimeter on the outer aspects of the anterior superior iliac spines of the ilium. The instrument was held so that it was parallel with the ground.

MEASUREMENT OF THE HEAD. Three measurements were taken, namely, circumference, head length and head breadth. With the girls it was often necessary to remove clasps, kirby grips, ribbons, hair nets, undo plaits and re-distribute the hair so that it lay evenly. The children were seated. The measurement was recorded to the nearest half centimetre.

Circumference. A thin flexible steel tape was employed and the observations taken from the front. The surface markings used were the external occipital protuberance and the glabella.

Head Length. The subject looked to the front and the examiner stood at the side. One tip of the pelvimeter blade was placed on the glabella and the other swept to and fro over the external occipital protuberance in the

antero-posterior axis. The maximum reading was taken.

Head Breadth. With the subject in the same position the examiner moved round facing him, placing the two points of the calipers above the ears, i.e., just above the external auditory meatus. The calipers were moved vertically upwards and downwards to and from the vertex, and the maximum reading recorded.

Estimation of Maturity. Both sexes were graded in three clinical groups: 'non-pubescent' showing no signs of sexual development, 'adolescent' showing an advanced degree of maturity and the 'intermediate pubescent' sexually-developing group. The classification of the boys was determined by the criteria laid down by Ellis (1946). The onset of pubescence in the girls was taken to be breast enlargement, the earliest sign noted being vascularization and enlargement of nipple and areola. Since this normally precedes the appearance of pubic hair by approximately a year, it provides a reasonably reliable landmark without subjecting children to more detailed examination. 'Adolescence' was reached at the onset of menstruation.

Results

Much of the work of compiling and analysing the results was done by the statistical section of the Department of Social Medicine.

Tables 1 and 2 present the statistical findings of the anthropometric study described in year-age groups from 5 to 18 in the two sexes. The numbers of children measured in each age group are given, together with the central age of the group. Three

TABLE 1

STRATIFIED SAMPLE OF EDINBURGH BOYS

Year Age Group	No.	Statistic	Age (years)	Length (cm.)	Crown-Rump (cm.)	Span (cm.)	Crown-Rump/ Length Ratio	Span
5+	56	Mean	5·51	109·3	62·6	107·2	0·573	0
		S.D.	0·256	4·90	2·97	5·45	—	
		C.V.	0·046	0·045	0·048	0·051	—	
6+	67	Mean	6·50	115·4	64·9	114·3	0·564	0
		S.D.	0·282	6·15	3·03	6·82	—	
		C.V.	0·043	0·053	0·047	0·060	—	
7+	55	Mean	7·59	122·1	67·5	121·6	0·554	0
		S.D.	0·263	5·85	2·90	5·98	—	
		C.V.	0·035	0·048	0·043	0·049	—	
8+	63	Mean	8·46	125·2	68·5	125·2	0·548	1
		S.D.	0·294	5·12	2·73	5·45	—	
		C.V.	0·035	0·041	0·040	0·044	—	
9+	60	Mean	9·51	130·5	70·8	130·5	0·543	1
		S.D.	0·326	5·92	2·59	5·99	—	
		C.V.	0·034	0·045	0·037	0·046	—	
10+	63	Mean	10·51	136·0	72·8	135·9	0·540	1
		S.D.	0·269	6·07	2·54	7·16	—	
		C.V.	0·026	0·045	0·035	0·053	—	
11+	60	Mean	11·60	141·3	75·3	141·5	0·533	1
		S.D.	0·266	6·66	3·41	6·86	—	
		C.V.	0·023	0·047	0·045	0·048	—	
12+	80	Mean	12·57	148·1	77·8	148·3	0·526	
		S.D.	0·283	7·94	3·65	7·76	—	
		C.V.	0·023	0·054	0·047	0·052	—	
13+	85	Mean	13·47	152·5	79·9	153·5	0·526	
		S.D.	0·284	8·81	4·14	9·70	—	
		C.V.	0·021	0·058	0·052	0·063	—	
14+	84	Mean	14·54	159·4	83·3	160·7	0·524	
		S.D.	0·291	9·09	4·64	9·62	—	
		C.V.	0·020	0·057	0·056	0·060	—	
15+	93	Mean	15·40	167·2	87·7	168·3	0·525	
		S.D.	0·300	8·70	4·99	11·52	—	
		C.V.	0·019	0·052	0·057	0·068	—	
16+	69	Mean	16·57	173·5	91·6	176·3	0·528	
		S.D.	0·300	8·31	4·68	8·94	—	
		C.V.	0·018	0·048	0·051	0·051	—	
17+	61	Mean	17·47	173·7	92·4	176·7	0·532	
		S.D.	0·303	6·88	3·63	6·95	—	
		C.V.	0·017	0·040	0·039	0·039	—	

S.D. = Standard deviation from mean. C.V.

ratios are included in the table, i.e., crown-rump length/length, span/length and head breadth/head length (cephalic index). Figs. 1 to 4 show graphically the means of three linear measurements (length, stem-length and span) and two measurements of width (bi-acromial diameter and intraspinous pelvic width) for the two sexes.

Comment

Length. In the present study, supine crown-heel length was measured in preference to erect height for two reasons. The first was that recumbent length measurements are essential in infants and that correct positioning for measurement of erect height in toddlers and pre-school children is even more difficult than for recumbent length. In order to provide a continuous series of measurements from birth to maturity, it is desirable that all should be obtained in the same way. Secondly, it has been shown (Palmer, 1932) that posture is likely to affect measurements of erect height to a greater extent in girls than boys, particularly in the case of adolescents. It cannot be claimed that the recumbent position altogether eliminates the errors introduced by measuring erect height at different times of day, since diurnal variations are also substantial in measurements of recumbent length (Kelly, Sonders, Johnston, Bound, Hunscher and Macy, 1943). It can reasonably be assumed, however, that these

TABLE 1

F EDINBURGH SCHOOL CHILDREN, 1951/53

BOYS

Rump/ th io	Span/Length Ratio	Weight (kg.)	Bi-acromial Diameter (cm.)	Pelvic Width (cm.)	Head Circumference (cm.)	Head Length (cm.)	Head Breadth (cm.)	Cephalic Index
73	0·980	19·01	24·47	18·42	51·15	17·77	13·87	0·781
	—	2·10	1·15	1·07	1·42	0·603	0·518	—
	—	0·110	0·05	0·06	0·03	0·03	0·04	—
54	0·991	21·05	25·66	19·04	51·83	17·93	14·06	0·786
	—	2·82	1·47	1·11	1·24	0·647	0·457	—
	—	0·134	0·06	0·06	0·02	0·04	0·03	—
54	0·996	23·83	26·75	19·92	52·19	18·12	14·18	0·783
	—	2·64	1·09	1·17	1·28	0·577	0·434	—
	—	0·111	0·04	0·06	0·02	0·03	0·03	—
48	1·000	25·23	27·66	20·75	52·37	18·14	14·23	0·785
	—	2·83	1·17	1·08	1·39	0·625	0·490	—
	—	0·112	0·04	0·05	0·03	0·03	0·03	—
43	1·001	27·50	28·44	20·99	52·69	18·19	14·35	0·789
	—	3·27	1·45	1·15	1·26	0·576	0·425	—
	—	0·119	0·05	0·05	0·02	0·03	0·03	—
40	1·007	30·25	29·40	21·98	52·97	18·39	14·41	0·785
	—	3·84	1·58	1·14	1·52	0·638	0·528	—
	—	0·127	0·05	0·05	0·03	0·03	0·04	—
33	1·002	33·42	30·46	22·74	53·42	18·41	14·57	0·793
	—	5·06	1·85	1·37	1·23	0·635	0·500	—
	—	0·151	0·06	0·06	0·02	0·03	0·03	—
26	1·003	37·04	31·45	23·63	53·89	18·60	14·59	0·785
	—	5·62	1·81	1·52	1·38	0·643	0·516	—
	—	0·152	0·06	0·06	0·03	0·03	0·04	—
26	1·007	41·96	32·86	24·38	54·13	18·65	14·78	0·793
	—	7·85	2·18	1·76	1·37	0·676	0·472	—
	—	0·187	0·07	0·07	0·03	0·04	0·03	—
24	1·009	45·98	34·17	25·48	54·58	18·77	14·87	0·792
	—	7·82	2·45	1·78	1·53	0·637	0·521	—
	—	0·170	0·07	0·07	0·03	0·03	0·04	—
25	1·011	54·57	36·27	26·73	55·61	19·21	14·95	0·779
	—	8·89	2·47	1·61	1·77	0·825	0·664	—
	—	0·163	0·07	0·06	0·03	0·04	0·04	—
28	1·017	60·57	37·94	27·64	56·56	19·45	15·28	0·786
	—	8·35	1·99	1·59	1·34	0·642	0·585	—
	—	0·138	0·06	0·06	0·02	0·03	0·04	—
32	1·019	62·46	38·30	27·89	56·62	19·57	15·43	0·790
	—	9·70	1·87	1·26	1·50	0·692	0·670	—
	—	0·155	0·05	0·05	0·03	0·04	0·04	—

n mean. C.V. Coefficient of variation.

variations, which are at least partly due to fatigue and posture, will be reduced by measuring length in the recumbent position. Comparisons between stem-length and crown-heel length will only be valid when both are taken in the same position (i.e., recumbent or erect), and again accurate positioning for stem-length is more readily achieved in children in the recumbent than in the erect position.

The use of recumbent length does, however, introduce a discrepancy when comparing data obtained by this method with other series in which erect height has been measured. Boyd (1929) found that supine length was 1 to 1½ cm. greater than erect height in children aged 2 to 5 years, and Palmer (1932) made a detailed comparison of the relationship of the two measurements in older children, constructing conversion tables for each sex, which give the calculated erect height for any given value of supine length from 80 to 180 cm. For supine length 110 cm., erect height was found to be 1·0 cm. less in the case of boys and 1·05 less in the case of girls. Over the range 111 cm. to 180 cm. supine length, the mean differences from erect height were found to be 0·5 cm. (boys) and 1·1 cm. (girls). In practice, subtraction of these amounts from supine length will give an approximate value for erect height which will lie within the experimental error of routine measurements of height, but for

TABLE 2

STRATIFIED SAMPLE OF EDIN

GIRLS

Year Age Group	No.	Statistic	Age (years)	Length (cm.)	Crown-Rump (cm.)	Span (cm.)	Crown-Rump/ Length Ratio
5+	48	Mean	5·60	110·4	62·5	107·6	0·568
		S.D.	0·237	4·99	2·50	5·34	—
		C.V.	0·042	0·045	0·040	0·050	—
6+	61	Mean	6·54	115·6	64·5	113·7	0·559
		S.D.	0·263	5·97	2·92	6·66	—
		C.V.	0·040	0·052	0·045	0·059	—
7+	58	Mean	7·49	121·1	66·9	119·4	0·553
		S.D.	0·281	5·18	2·65	5·42	—
		C.V.	0·038	0·043	0·040	0·045	—
8+	57	Mean	8·49	125·4	68·8	123·4	0·550
		S.D.	0·287	6·30	3·15	6·20	—
		C.V.	0·034	0·050	0·046	0·050	—
9+	56	Mean	9·51	130·2	70·3	129·7	0·541
		S.D.	0·294	6·13	2·89	6·91	—
		C.V.	0·031	0·047	0·041	0·053	—
10+	63	Mean	10·48	135·4	72·6	134·8	0·538
		S.D.	0·253	7·18	3·41	7·27	—
		C.V.	0·024	0·053	0·047	0·054	—
11+	64	Mean	11·52	141·4	75·5	141·2	0·535
		S.D.	0·289	7·11	3·41	7·40	—
		C.V.	0·025	0·050	0·045	0·052	—
12+	79	Mean	12·54	148·4	79·2	148·3	0·534
		S.D.	0·296	7·18	3·73	7·95	—
		C.V.	0·024	0·048	0·047	0·054	—
13+	75	Mean	13·49	155·1	83·3	155·5	0·538
		S.D.	0·299	7·43	4·43	8·30	—
		C.V.	0·022	0·048	0·053	0·053	—
14+	62	Mean	14·51	157·1	84·6	157·9	0·540
		S.D.	0·302	7·47	4·05	7·61	—
		C.V.	0·021	0·048	0·048	0·048	—
15+	86	Mean	15·40	162·1	87·7	163·2	0·541
		S.D.	0·307	5·30	3·19	5·69	—
		C.V.	0·020	0·033	0·036	0·035	—
16+	69	Mean	16·48	162·8	87·8	164·6	0·540
		S.D.	0·265	5·33	2·89	5·45	—
		C.V.	0·016	0·033	0·033	0·033	—
17+	56	Mean	17·46	164·3	89·9	164·4	0·548
		S.D.	0·305	6·66	3·28	6·65	—
		C.V.	0·017	0·041	0·037	0·040	—

S.D. = Standard deviation from the mean.

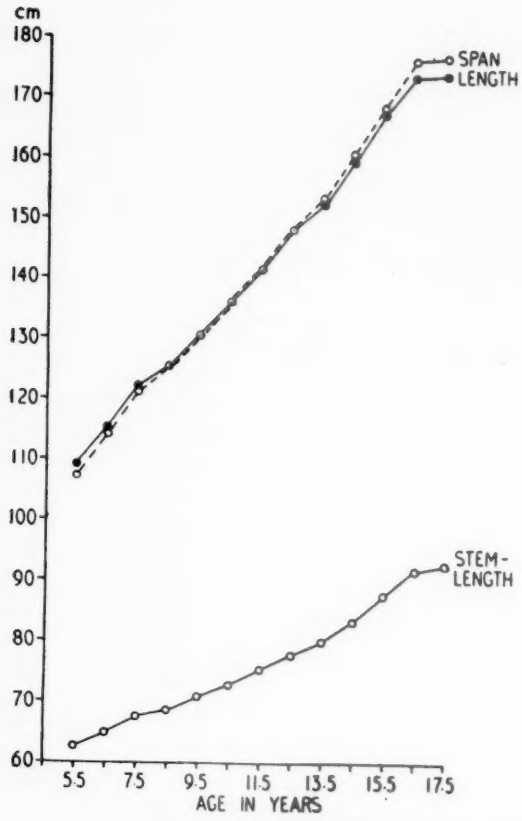
more accurate assessment Palmer's conversion tables should be used.

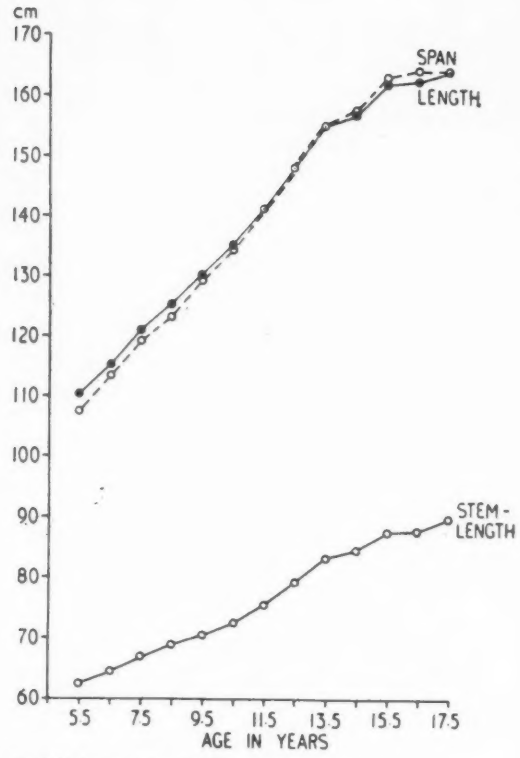
In most recorded data on children's heights and weights it has been found that these measurements of girls are less than those of boys at all ages except for a period lasting approximately from $11\frac{1}{2}$ to $13\frac{1}{2}$ or $14\frac{1}{2}$ years; during this time the earlier age-onset of puberty causes girls to grow more rapidly and equal or exceed boys in height and weight. In the later teen-ages, growth in height of girls decelerates rapidly and their stature is again exceeded by that of boys. In the present series, it will be seen that the mean length of girls equals or exceeds that of boys between the ages of 11 and 14 years, and that from 14 to 18 years boys are significantly taller and from 15 to 18 significantly heavier. The present figures, however, do not demonstrate a consistent sex-difference in recumbent length in the younger age groups, though with the exception of one group (aged 9>10 years) the mean weight of boys is greater than that of girls from 5 to 11 years, and the means for stem-length and span tend to be slightly (but not consistently) greater. It should be emphasized that the sex-differences in average erect height observed in other series of younger children are often very small, e.g., 0·6 to 1·1 cm. in London schoolchildren 5 to 11 years (Daley, 1950), and measurement of recumbent length appears to

BURGH SCHOOL CHILDREN, 1951/53

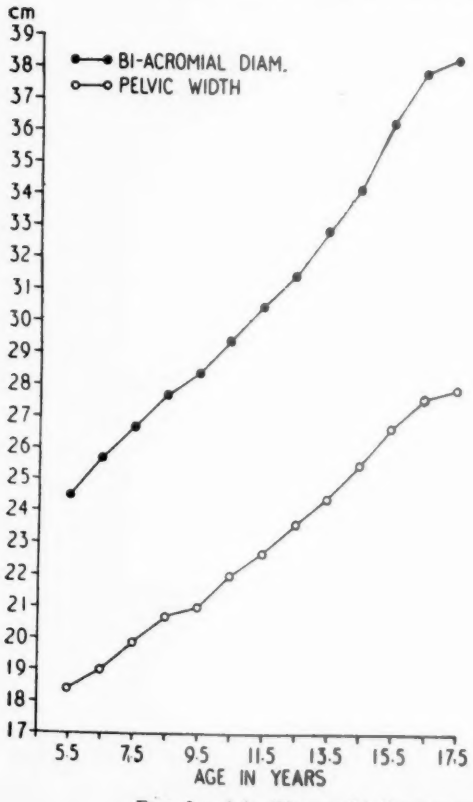
Span/Length Ratio	Weight (kg.)	Bi-acromial Diameter (cm.)	Pelvic Width (cm.)	Head Circum-ference (cm.)	Head Length (cm.)	Head Breadth (cm.)	Cephalic Index
0·974	18·90	24·72	18·14	50·50	17·29	13·70	0·792
—	2·19	1·26	1·04	1·34	0·609	0·48	—
—	0·116	0·05	0·06	0·03	0·04	0·04	—
0·984	20·84	25·66	18·89	51·25	17·59	13·73	0·781
—	3·53	1·48	1·17	1·54	0·668	0·545	—
—	0·169	0·06	0·06	0·03	0·04	0·04	—
0·987	23·25	26·81	19·87	51·57	17·76	13·97	0·788
—	3·17	1·40	1·17	1·34	0·579	0·467	—
—	0·136	0·05	0·06	0·03	0·03	0·03	—
0·985	24·76	27·27	20·38	51·52	17·78	13·95	0·785
—	3·12	1·27	1·06	1·23	0·575	0·460	—
—	0·126	0·05	0·05	0·02	0·03	0·03	—
0·997	27·85	28·53	21·06	52·13	17·90	14·06	0·787
—	4·28	1·70	1·29	1·20	0·636	0·448	—
—	0·154	0·06	0·06	0·02	0·04	0·03	—
0·997	29·59	29·25	21·70	52·23	17·80	14·11	0·793
—	4·21	1·60	1·30	1·38	0·657	0·470	—
—	0·142	0·05	0·06	0·03	0·04	0·03	—
0·999	33·84	30·66	22·92	52·97	18·04	14·21	0·789
—	5·09	1·83	1·33	1·49	0·720	0·518	—
—	0·150	0·06	0·06	0·03	0·04	0·04	—
1·000	38·88	32·14	24·08	53·33	18·13	14·30	0·791
—	6·01	1·75	1·52	1·38	0·623	0·569	—
—	0·155	0·05	0·06	0·03	0·03	0·04	—
1·002	44·82	33·66	25·22	53·75	18·25	14·27	0·783
—	7·46	1·77	1·70	1·30	0·578	0·522	—
—	0·166	0·05	0·07	0·02	0·03	0·04	—
1·007	48·06	34·27	25·97	54·16	18·30	14·49	0·793
—	8·42	1·82	1·71	1·62	0·662	0·516	—
—	0·175	0·05	0·07	0·03	0·04	0·04	—
1·007	52·93	35·16	26·98	54·51	18·53	14·56	0·786
—	7·79	1·73	1·30	1·39	0·676	0·50	—
—	0·147	0·05	0·05	0·03	0·04	0·03	—
1·010	54·60	35·71	27·22	54·85	18·71	14·66	0·784
—	6·60	1·61	1·08	1·42	0·597	0·496	—
—	0·121	0·05	0·04	0·03	0·03	0·03	—
1·001	56·97	35·79	28·03	54·85	18·72	14·93	0·797
—	8·20	1·99	1·82	1·36	0·687	0·677	—
—	0·144	0·06	0·06	0·02	0·04	0·05	—

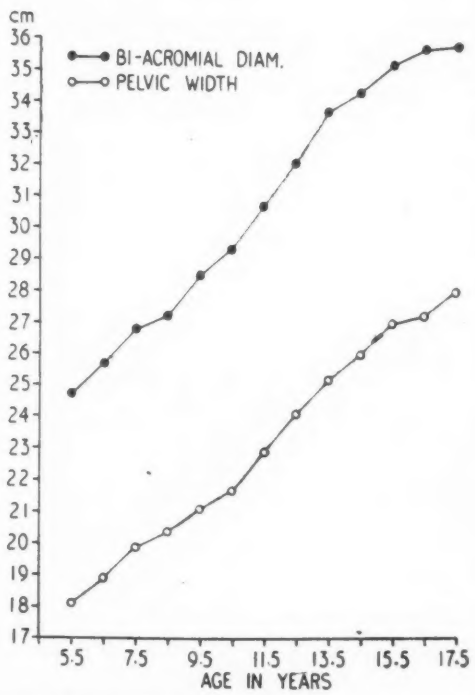
C.V. = Coefficient of variation.





FIGS. 1 and 2.—Length, stem length and span compared in boys (Fig. 1) and girls (Fig. 2).





FIGS. 3 and 4.—Bi-acromial diameter and pelvic width compared in boys (Fig. 3) and girls (Fig. 4).

reduce or eliminate them. Thus, in Simmons' (1944) longitudinal study in which both erect height and recumbent length were measured on the same children, the recumbent length measurements are not consistently greater in boys than girls aged 5 to 9 years, although the measurements of erect height are greater for boys at each of these ages.

Comparison with Other Data. Stein (1953) found that in one working-class ward in Edinburgh in 1951/52 the means of height and weight of primary schoolchildren up to 12 years of age were lower than those found in London in 1949 (Daley, 1950). Using length adjusted for erect height, the present series confirms that samples of Edinburgh boys and girls are shorter than London schoolchildren up to the age of 12 years, but that from 12 to 15 years the heights of boys in both cities are closely similar, and that those of older Edinburgh girls approximate more nearly to the London figures. It should, however, be pointed out that the Edinburgh samples contain a slightly increased proportion of fee-paying pupils between 11 and 15 years. A comparison of weights at first suggests that the Edinburgh boys are on the average 1·15 kg. lighter and girls 1·39 kg. lighter than the London schoolchildren through the age-range 5 to 15 years, but an important discrepancy is introduced by the fact that the present series represents unclothed weights. Daley (1950) does not state whether the weights he quotes were unclothed weights, but as he compares these with the 1938 London figures and these are stated to be weights taken in indoor clothing without shoes (Menzies, 1940), it may be assumed that Daley's weights include clothing. A part (and possibly the major part) of the difference between the weights in the Edinburgh and London series is therefore attributable to clothing. This illustrates the necessity of recording techniques as well as analyses of data when comparisons between different series of children's measurements are made, particularly when the observed differences are relatively small.

A more satisfactory comparison can be made with various American data in which unclothed weight is recorded, together with stem-length, shoulder-width, etc. For example, the figures given by Meredith and Meredith (1953) for Oregon children, more than 50% of whom were of British descent, do indicate significant differences from the Edinburgh children. Thus Oregon boys aged 10 years were more than 2·7 cm. taller and 2·6 kg. heavier than Edinburgh boys with a central age of 10·5 years. Oregon girls aged 11 years were more than 3 cm. taller and 3·7 kg. heavier than the Edinburgh girls with a central age of 11·5 years. The measurements of stem-length and shoulder-width also favoured the Oregon children, although the differences were relatively smaller.

Sexual Maturation. It has been repeatedly affirmed that the greater heights and weights of children of all ages which are commonly reported to-day compared, for instance, with those of similar groups 25 or more years ago, are at least partly due to earlier maturation. While radiological assessment of skeletal age (Todd, 1937) probably provides the most reliable index of maturation, such data are seldom available in earlier studies, and clinical assessment of age-onset of the various stages of sexual maturation (pubescence, menarche, etc.) still has considerable value.

From the figures given in Table 3, the median age of pubescence (i.e., the age at which 50% of the children were found to be non-pubescent and 50% pubescent or more mature) and the median age of 'adolescence' (i.e., advanced sexual maturity in boys and onset of menstruation in girls) was calculated for each sex to the first approximation of probit

TABLE 3
MATURITY GRADING

BOYS

Mean age (years)	5·51	6·50	7·59	8·46	9·51	10·51	11·60	12·57	13·47	14·54	15·40	16·57	17·47
Number	56	57	55	63	60	63	60	80	85	84	93	69	61
% Non-pubescent	100	100	100	100	100	100	95	77·5	47·1	21·4	6·5	1·4	0
% Pubescent	0	0	0	0	0	0	5	22·5	49·4	60·7	37·6	11·6	1·6
% Adolescent	0	0	0	0	0	0	0	0	3·5	17·9	55·9	87·0	98·4

GIRLS

Mean age (years)	5·60	6·54	7·49	8·49	9·51	10·48	11·52	12·54	13·49	14·51	15·40	16·48	17·46
Number	48	61	58	57	56	63	64	79	75	62	86	69	56
% Non-pubescent	100	100	100	100	94·6	79·4	46·9	11·4	1·4	0	0	0	0
% Pubescent	0	0	0	0	5·4	20·6	53·1	81·0	45·3	21·0	7·0	1·4	1·8
% Adolescent	0	0	0	0	0	0	0	7·6	53·3	79·0	93·0	98·6	98·2

analysis. Where comparisons are made with the data of Hogben, Waterhouse and Hogben (1948) the figures quoted are those obtained by probit analysis, although these authors expressed a preference for the logistic fit which gave somewhat lower values. Bryan and Greenberg (1952), however, who analysed their data on sexual maturation of girls by probits, logits and Karber's method, found that the three methods gave closely similar results, and considered that the first two held no advantage over Karber's method of calculating maturity points. The last method only was used by Bryan and Greenberg in determining the maturity of boys.

BOYS. The median age of pubescence was found to be 13·45 years and that of adolescence 15·35 years. The first of these figures corresponds closely with that given by Ellis (1948) for boys in two residential schools in England, viz., 13·4 years where the same criteria were used and is comparable with the figure of $13 \cdot 6 \pm 1 \cdot 05$ years based on the presence or absence of pubic hair used by Hogben *et al.* (1948). Bryan and Greenberg (1952), who used Ellis's criteria in grading boys, gave 13·1 years as the 50% immaturity point in their American study. The duration of pubescence at median age would thus be 1·9 years in the present series compared with approximately 1·2 years in the first English series. Ellis's figures suggested that the duration of pubescence was longer in the case of boys reaching pubescence early or late. Graphic representation of the present figures for boys non-pubescent and non-adolescent gives some support to this view as far as the boys reaching pubescence early are concerned, viz., 2·2 years when pubescence is reached at 11·5 years and 2·1 years when reached at 12·5 years, but for those reaching pubescence at 14·5 years the duration is approximately 1·7 years, i.e., less than at the median age. Since the curves in the present series are considerably more symmetrical than the English series (where the upper age groups were supplemented by boys in employment from a different sample) it appears probable that a longer duration of pubescence in boys who mature late is not a consistent finding. As was pointed out, however, duration of pubescence in early and late maturing boys can only be accurately assessed by longitudinal studies.

GIRLS. The median age of reaching pubescence, as indicated by evidence of breast development, was 11·30 years and of adolescence (menarche) 13·35 years. The first figure corresponds fairly closely with that given by Hogben *et al.* (1948) for English schoolgirls, viz., $11 \cdot 5 \pm 0 \cdot 83$ years, but is significantly later than the age given by Bryan and Greenberg (1952) for American schoolgirls, viz., $10 \cdot 6 \pm 0 \cdot 24$ years. Considerably more comparative data exist for both the mean and median age of menarche, and since there is evidence that the distribution of age of menarche is approximately symmetrical (Ellis, 1947; Wilson and Sutherland, 1950), it is possible to compare the median age in the present series with either the mean or median of other British series, e.g., median $13 \cdot 49 \pm 1 \cdot 19$ years in 2,590 day-school pupils (Wilson and Sutherland, 1950). Again it will be seen that there is reasonably close correspondence between the Edinburgh figures and recent data collected in England. The calculated duration of pubescence at median age in the Edinburgh series is 2·05 years, which may be compared with the figure of 2·5 years given by Hogben *et al.* (1948) as the time interval between the appearance of breast development and the onset of menstruation.

Sex Differences in Maturation. These figures give clear confirmation to the observations of previous authors (e.g., Cawley, Waterhouse and Hogben, 1949) that boys begin to show evidence of sexual maturation on the average two years (here 2·1 years) later than girls. Furthermore, the clinical assessment of the later stage of maturity described as 'adolescence', which is admittedly somewhat arbitrary and subjective in the case of boys, defines a median value which in this series falls exactly two years later than the median age of the menarche in girls. The maintenance of this two-year sex difference suggests that the criteria adopted for defining 'adolescence' in boys (Ellis, 1946) do have

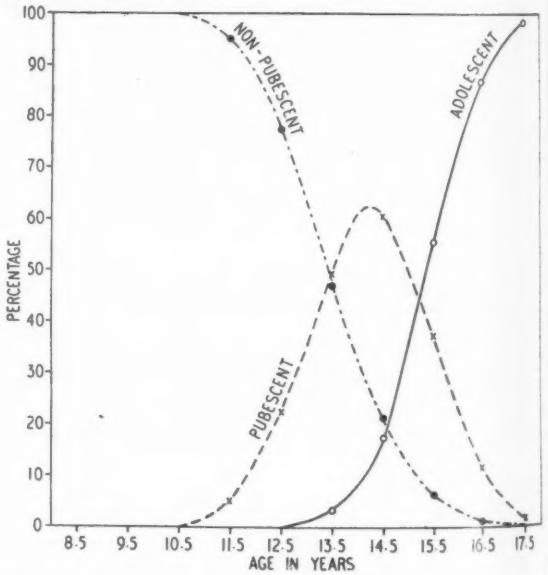


FIG. 5.—Percentage of boys non-pubescent, pubescent and adolescent in each year of age.

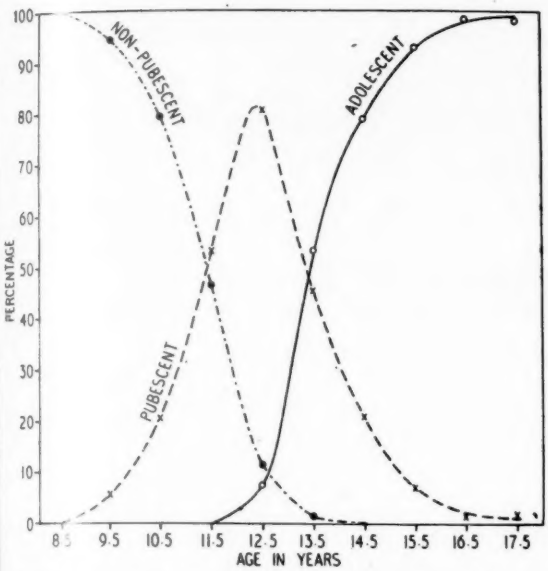


FIG. 6.—Percentage of girls non-pubescent, pubescent and adolescent in each year of age.

a practical value in assessing a stage of male maturity corresponding approximately to the menarche in girls. Figs. 5 and 6 show the results graphically, from which it will be seen that whilst the general pattern of maturation is similar in the two sexes, the corresponding stages of development are reached on the average two years later in boys than in girls.

Secular Changes in Maturation. In 1933, Kennedy published data on the mean age of the menarche of women resident in Edinburgh or its environs, based on an analysis of 10,219 hospital records. Although hospital patients cannot be accepted as a normal population, and the data would cover a considerable period before the date of publication, since most of the women were middle-aged at the time of the enquiry, the fact that the mean age of the menarche was found to be 15·037 years with a standard deviation of 1·707 years strongly indicates that sexual maturation in Edinburgh schoolgirls is now occurring significantly earlier than at the beginning of the century. There are no reliable data for this period relating to Edinburgh boys, but it has been observed since the days of the Talmud that boys mature later than girls, and many early writers have estimated the sex difference as 18 months to two years. Since the same sex-difference appears in the 1951/53 figures, it may reasonably be assumed that boys are also maturing earlier.

This earlier maturation, and the associated increase in mean heights and weights of school-children, are presumably due largely to improvement in nutrition and socio-economic conditions in the intervening years. It should be borne in mind, however, that attainment of maturity, at whatever age it occurs, is followed by rapid deceleration and cessation of growth, and that terminal or adult stature will be reached sooner in children who mature early. It would seem that although both speed of maturation and terminal height are genetically controlled, environment can influence the former to a relatively greater extent than it can adult stature.

Summary and Conclusions

Anthropometric data on 1,730 Edinburgh schoolchildren are presented. Nine body measurements were made on each child. Ratios are given for stem-length/crown-heel length, span/crown-heel length and cephalic index.

The methods of sampling, measurement, analysis and grading maturity are described.

The measurement of recumbent crown-heel length is discussed and compared with that of erect height.

The results of maturity grading are compared with those of other recent British studies, and contrasted with earlier Edinburgh data on the age of the menarche.

The present study supports the view that schoolchildren are maturing earlier now than at the beginning of the century.

This investigation was undertaken during the tenure of a Guthrie Research Fellowship by H.S.P. We are indebted to J. N. Mansbridge for his help and collaboration throughout; to Mrs. Mansbridge and Miss Yates for the laborious recording of data; to Dr. Boog Watson, Chief School Medical Officer of the City, for his unfailing help, and to the headmasters, headmistresses and pupils of the schools concerned for making the investigation possible. We are also most grateful to Dr. L. Stein and the statistical staff of the Department of Social Medicine for statistical analyses.

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A NEW HEREDO-FAMILIAL NEUROLOGICAL SYNDROME

BY

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This report describes a family in which a heredo-familial neurological disorder of unusual type appears to have been transmitted from an affected father to at least five of his children. The main features of the condition consisted of athetosis, hypotonia, absent tendon reflexes, extensor plantar responses, mental retardation and periodic febrile attacks occurring simultaneously in several members of the family with episodes of prolonged unconsciousness.

Ford (1952) gave an account of the various hereditary and familial encephalomyelitic and demyelinating diseases, but none of the clinical syndromes he described correspond with our cases, nor have we been able in a search of the literature to find records of cases similar to our own. We therefore present the following case reports in the belief that they represent a hitherto undescribed disease.

Case Reports

The family first came to our notice on December 8, 1948. The mother, a woman of low intelligence, was born in 1915. She has no neurological disorder. She had given birth during her first marriage to four children who are neurologically healthy individuals. After the death of her husband she married a man born in 1904, who since childhood had suffered from a neurological disability, and is considered unable to work. Our only information about his earlier years is that he was late in walking, was mentally backward and had no schooling after the age of 7. In August, 1951, at the age of 47, he was examined by Dr. Sheila Sheehan. He was found to have pes cavus, kyphoscoliosis and severe athetosis which amounted almost to torsion spasm. He had extensor plantar responses, absent tendon reflexes and some wasting of the shoulder girdle muscles. The picture resembled Friedreich's ataxia or some allied heredo-familial disorder, but there was athetosis and there were no cerebellar signs. His family could not be traced. Little is known about them, except that his father and siblings were all well, but his mother had some difficulty in walking.

Case 1. This boy, the first child of the second husband, was born on October 25, 1942. His progress was subnormal throughout. He was examined by a paediatric colleague at the age of 5¼ years on January 26, 1948, and was found to have choreo-athetosis, with gross mental deficiency. There was no response to intelligence testing and he was certified as a mental defective. His hearing and vision were thought to be normal. On September 11, 1948, at the age of 5 years 11 months he died in a fever hospital of what was reported to be pneumonia following measles. Necropsy showed bilateral bronchopneumonia. The central nervous system was not examined. There was no record of any abnormality in the liver.

At the time of this illness three younger siblings also became ill.

Case 2. The second child of this marriage, a boy, was born on June 8, 1944, weighing 5¼ lb. (2·3 kg.). He grasped objects only at 1 year, was very late sitting up and his mother described him as 'shaky' in infancy. Up to the age of 4 years he had never walked more than a few steps without support and had only begun to say single words at 3½ years.

In September, 1948, when he was 4¼, he developed at the same time as his brother (Case 1) an acute febrile illness with a rash, which was diagnosed as measles. Two days after the appearance of the rash his eyes turned up and he became unconscious but he had no fit. He failed to recognize his mother for a week and his general condition deteriorated. Subsequently, his legs became weaker and he was no longer able to walk, even with support. He became more 'shaky' and 'jumpy' and his speech became more indistinct. When we first examined him on December 18, 1948, three months after his 'measles', he was emaciated, weighing 25½ lb. (11·5 kg.). The haemoglobin was 55% (Sahli). He exhibited generalized athetosis. He did not respond to simple questions and was considered to be mentally retarded. By the age of 6 years he was able to walk with the support of furniture and made some attempt to feed himself. There appeared to be no improvement in his condition during the next two years and he did not attend school.

He was seen in the Children's Hospital, Sheffield, in July, 1951. He then had gross athetosis and was unable

to stand or walk. It was difficult to assess the tendon reflexes, but they were thought to be present. The plantar responses were flexor and the abdominal reflexes were present. The optic fundi were normal. Intelligence testing was difficult because of the athetosis, but his attention was well held. No accurate figure for his intelligence quotient could be given, but it was thought to be about 50.

He received physiotherapy and speech therapy with considerable improvement. Subsequently he was admitted to a convalescent home where this treatment was continued, and where he was given suitable schooling for an educationally subnormal child. While he was there he received 'artane', 1 mg. twice daily, for six months without obvious improvement.

His condition was reassessed in August, 1954, at the age of 10 years. His nutrition was good and he was happy and cooperative. He had gross generalized hypotonia, muscular weakness and pronounced athetosis. His speech was intelligible but dysarthric. All tendon reflexes were now absent and the plantar responses were extensor. The upper abdominal reflexes were present but the lower ones absent. The fundi were normal and there were no apparent sensory changes. There were no cerebellar signs. He was barely able to stand unaided and could not walk (Fig. 1). He had no Kayser-Fleischer rings on slit-lamp examination of his eyes.

FIG. 1.

His intelligence was reassessed (Terman-Merrill) and the I.Q. was 51. He cooperated well, but his physical disability may have been in small part responsible for his low score. An electroencephalogram was normal. Liver function tests, a blood Wassermann reaction and tests for toxoplasmosis gave normal results. There was no excess of amino-acids in the urine.

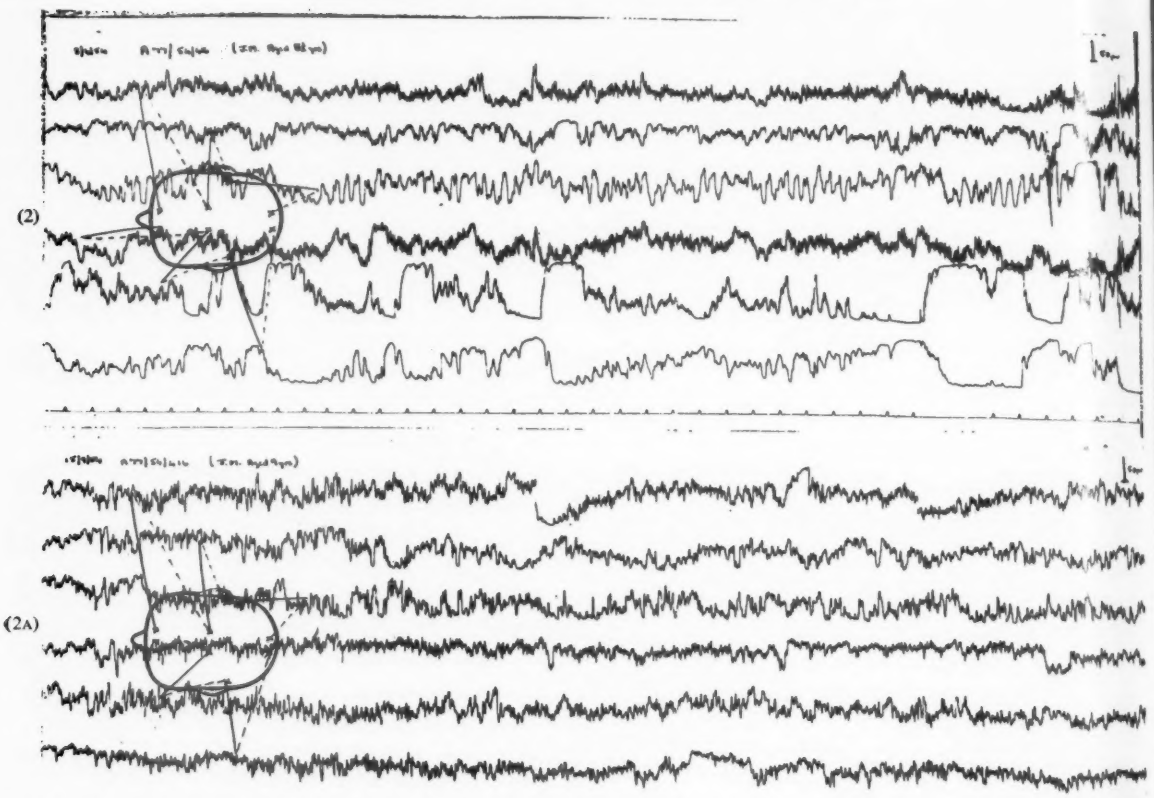
Case 3. The third affected child was a girl born at full term on June 3, 1945, weighing 6½ lb. (3 kg.) after a normal pregnancy and delivery. She was said to have developed fairly normally at first, sitting unsupported at 8 or 9 months and first walking unaided between 12 and 18 months. She was said to have walked, run and played normally and to have said simple sentences until she developed, in September, 1948, the illness which in her case also was diagnosed as measles. She was then 3¼ years old. Following this illness she deteriorated mentally and became unable to walk. She was first examined by one of us with her two affected brothers (Cases 2 and 4) on December 8, 1948, at the age of 3 years 6 months. She was as severely malnourished and debilitated as her brothers, and weighed only 25¾ lb. (11·6 kg.). She displayed appreciable athetosis. Two months later her sitting posture was still unsteady, though she had started walking with difficulty. She was using a few simple words. Two years later, in November, 1950, at the age of 5½ years, she was using short sentences, but her speech was indistinct. She walked very unsteadily with assistance on a broad base. She had considerable athetosis, especially of the left hand. At 6½ years of age she was walking unsteadily on her own. In April, 1952, when aged 6 years 10 months, she attended the Sheffield Children's Hospital as an outpatient, when she was found to be considerably mentally retarded, could not walk without support and was said to have only recently acquired control over bowel and bladder. The tendon reflexes in the arms and legs were diminished and the plantar responses were flexor.

On March 26, 1954, another illness struck her and she became ill with a sore throat, red eyes, irritability, anorexia and vomiting (see also Case 4). Two days later she was thought to be feverish and became semi-comatose. She was admitted to the Children's Hospital on March 31, 1954. She was then afebrile, comatose and poorly nourished, weighing only 38 lb. (17·1 kg.). She lay on her side in semi-coma with the head extended, the limbs flexed and with occasional athetoid movements of the arms. The muscle tone in the limbs was normal, but no tendon reflexes could be elicited. The left plantar response was extensor and the right flexor. Ocular movements appeared to be full and the fundi were normal. No other abnormality was found and the throat was not inflamed.

The following investigations gave normal results: cerebrospinal fluid, a radiograph of the skull and chest, urine, blood urea and serum proteins. An electroencephalogram (E.E.G.) on April 8, 1954, showed a continuous high-amplitude 1-3 cycle/second activity occurring synchronously in both posterior regions. The record suggested involvement of the diffuse reticular network, probably in the midbrain, or a posterior fossa lesion. (Fig. 2.)

There was little change in the child's general condition over the next few weeks. She always lay on her side with her legs flexed and resented interference. She showed no interest in her surroundings, and feeding was difficult. She was discharged on May 11, 1954, at the mother's request, and by then the athetosis was more pronounced.

She was seen again three months later, when she was fully conscious and cooperative, and had the same neurological features (Fig. 3) as her brother (Case 2). Inspection of the eyes revealed no Kayser-Fleischer rings. A second E.E.G. on September 15, 1954, showed considerable improvement, with residual abnormalities localized to the posterior region on the



FIGS. 2 and 2A.—Upper tracing taken on April 8, 1954, shows almost continuous moderate amplitude 2 c./sec. waves occurring synchronously in both posterior regions. This is consistent with a posterior fossa lesion.

In the lower tracing taken on September 15, these slow waves have disappeared, and the record now contains an abnormally wide range of frequencies, with an ill-defined, paroxysmal right temporal theta focus. This looks very much like an epileptic interseizure record with possibly a right temporal epileptogenic focus.

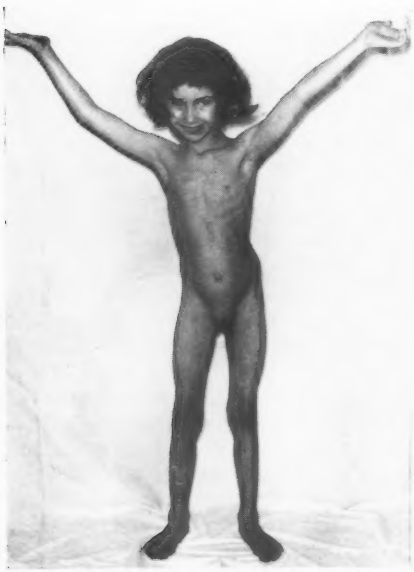


FIG. 3.

right side (Fig. 2A). The Wassermann reaction and liver function tests also performed about this time were normal. A toxoplasmosis dye test was positive in a titre of 1 in 49 and a complement fixation test was positive at 1 in 4. These results were not thought to be significant.

Case 4. This boy was born at full term on June 8, 1946, after a normal pregnancy and delivery. He weighed 7½ lb. (3·5 kg.). The neonatal period was uneventful. He was said to have walked at 18 months of age, but could never manage stairs. He used simple words at about the age of 2 years.

In September, 1948, when 2¼ years old, at the same time as his siblings (Cases 1, 2 and 3,) he developed a febrile illness with a rash. He was unconscious for an unknown period. When examined on December 8, 1948, at the age of 2½ years, he was very wasted and weighed 22 lb. 6 oz. (10 kg.). Neurological examination proved impracticable owing to his struggling. Two months later, he could stand holding the furniture, with the same unsteady, wobbling posture as the other children. At the age of 5 years he could only walk if supported, was unable to feed himself with a spoon and was incontinent. He was dysarthric and could only make three-word sentences. In August, 1951, when seen as an out-patient at Sheffield Children's Hospital, the abnormalities noted were general mental retardation, inability to walk unaided and diminution of the tendon reflexes. Six months later his plantar responses were

found to be extensor. At the age of 6 years, on July 22, 1952, he was unsteady and had athetosis, but less grossly than the older children. After that he is reported to have begun walking with support and talking more freely. His progress was then checked severely by a febrile illness, with sore throat, in April and May, 1953, during which he was in bed for seven weeks. His sister (Case 5) had a similar illness at the same time. Subsequently he could neither sit nor stand nor talk. When his two sisters (Cases 3 and 5) were admitted with the third acute family illness in March and April, 1954, though this boy was not seen at this hospital, the mother stated that he had had a similar illness with red eyes, sore throat, flushed cheeks and vomiting. His eyes rolled up, his arms were rigidly flexed, he failed to recognize his parents and could not swallow. He regained consciousness in about a week. The parents were unwilling for him to be admitted to hospital.

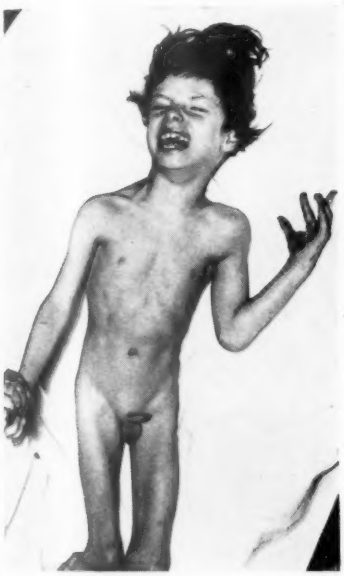


FIG 4.

He was seen again on August 25, 1954, when his general condition was found to be poor. He was conscious, wasted, hypotonic and was unable to sit or stand. Tendon reflexes were absent and the plantar responses were extensor (Fig. 4). Inspection of his eyes showed no Kayser-Fleischer rings. There was athetosis and he had a left internal strabismus. His blood Wassermann reaction, liver function tests and tests for toxoplasmosis all gave normal results. His E.E.G. was normal.

Case 5. The next affected child was a girl born at term on February 15, 1952, weighing 7 lb. 14 oz. (3·65 kg.). She was seen regularly at the baby clinic in the Sheffield Children's Hospital for the first year of life, and developed normally. She smiled at 6 weeks, pulled herself to the sitting position at 7 months and said single words at 11 months. She could shuffle across the floor at about 1 year of age. At 14 months of age, at the same time as her brother (Case 4), she had an acute illness, described as a 'sore throat', for which she was kept in a fever hospital for six weeks. 'Cerebral irritation' was noted: the cerebrospinal fluid was examined and was found to be normal. Two months after the onset of this illness she was seen again at the Children's Hospital and it was noted that she was very hypotonic, could no longer sit, crawl or pull herself into the standing position which she had previously been able to do. Her weight had been stationary for 5 months. She had a squint but no other neurological signs. After this she became able to sit unsupported, pulled herself up to stand and said individual words, but could not make sentences and could not walk.

She was not seen again until she was admitted to hospital on April 3, 1954, at the age of 2 years 1 month, with a similar history to Cases 3 and 4, namely, red eyes, sore throat and vomiting. Her eyes had rolled up and she had had twitching of the limbs at 15-minute intervals, followed by unconsciousness. Her mother said that this illness was very similar to the one she had had 11 months earlier.

On admission she was stuporose, but responded to painful stimuli and lay with the legs flexed. Her temperature was 100·4° F., rising to 104·2° F. The pupils were equal and reacted to light. The fundi were normal. There were no cranial nerve lesions, but she had a concomitant squint. There was no meningism. All limbs moved well but were hypotonic and no tendon reflexes could be elicited. The plantar responses were doubtful. Nothing abnormal was found in any other system.

INVESTIGATIONS. The cerebrospinal fluid was normal, including the Wassermann reaction and Lange curve.

The urine was normal, and an amino-acid chromatogram (April 8, 1954) was normal, apart from a possible slight excess of cystine. No reducing substance or phenyl-pyruvic acid was found.

The haemoglobin was 12 g./100 ml. with a leucocyte count of 13,000/c.mm. (72% neutrophil polymorphs, 24% lymphocytes, 4% monocytes). The blood urea, sugar and potassium levels were within normal limits.

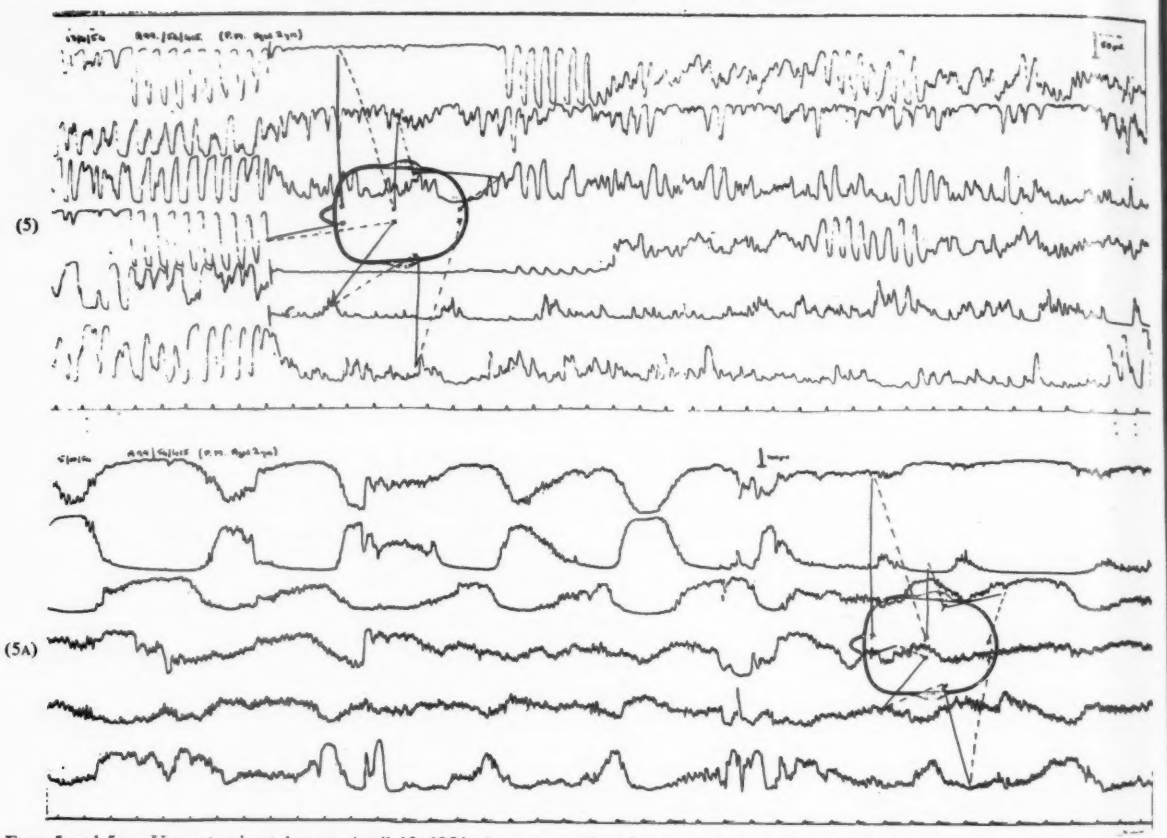
Liver function tests were within normal limits.

The Wassermann reaction (blood) was negative.

The serum proteins were: albumin 3·1 g./100 ml., globulin 2·8 g./100 ml.

A blood culture (× 4) was sterile.

CLINICAL COURSE AND TREATMENT. The degree of consciousness did not alter significantly during the five weeks that she was in hospital. Following admission, because it was at first thought likely that she might have an acute bacterial infection, she was treated with penicillin and streptomycin. The temperature slowly fell to normal over a period of seven days. When the antibiotics were discontinued four days later there was a sudden rise in temperature to 104·4° F. without apparent cause. As pulmonary complications were feared because of her prolonged coma, penicillin treatment was restarted and continued while she was in hospital. The temperature again settled and she remained afebrile. The plantar responses were found to be extensor on April 6, 1954, but the tendon reflexes remained absent. A week later she developed obvious athetoid movements for the first time. From then onwards her general condition did not alter.



FIGS. 5 and 5A.—Upper tracing taken on April 13, 1954, shows generalized bursts of high amplitude 1½-2 c/sec. waves occurring synchronously in all areas, suggesting involvement of the structures around the third ventricle or of the mid-brain.
In the lower tracing taken on October 5, 1954, these bursts of high amplitude slow waves have disappeared and the record is normal for her age.

An electro-encephalogram was performed on April 13, 1954, and was described as follows:

> 'There are frequent bursts of extremely high amplitude, generalized 2 cycles/second waves occurring synchronously in all areas. This suggests a lesion involving the reticular network, probably in the midbrain' (Fig. 5).

An air encephalogram on April 23, 1954, showed no gross hydrocephalus, but there was some widening of the sulci on the surface of the brain.

On May 11, 1954, she was sent home with her sister (Case 3).

She was seen again at her home on August 24, 1954. Her general condition had scarcely altered and she lived a vegetative existence. The physical signs had not changed. In October, 1954, she was more conscious. She had no Kayser-Fleischer rings. A second E.E.G. was performed and was found to be normal (Fig. 5A).

Summary of Case Reports

These five children all showed the same type of clinical syndrome and this in turn was similar to that of their father. It appears likely that three of them were of approximately normal physical and mental development in early infancy, but subsequently deteriorated and this deterioration was in four cases known to be preceded by acute febrile illnesses. There were three such known acute episodes in the family. The first in 1948 affected all four of the children then living (Cases 1-4). The second in 1953 affected two of the four then living children (Cases 4 and 5), and the third in 1954 affected three of the four children (Cases 3, 4 and 5); the remaining child (Case 2) was not then living at home. All of these episodes were of considerable severity and the first led to the death of one child (Case 1). Most of the others were associated with prolonged unconsciousness. Each child developed athetosis. In one (Case 1) we do not know of an acute febrile illness preceding it; in another (Case 2) athetosis was present after the first known febrile episode, but he may have had athetosis before that time before he came under our observation. The last three did not have athetosis until after one of these febrile episodes. There was severe mental deterioration immediately following each of the febrile episodes which we were able to observe, and there was a tendency for subsequent mental and

physical improvement until the onset of the next febrile episode. There was no progressive deterioration in any of the children under our observation. In those children whom we observed before these episodes there was no apparent hypotonia or abnormality of the reflexes, but every one of the survivors became grossly hypotonic with loss of deep tendon reflexes and with extensor plantar responses. There was no apparent sensory loss.

The only investigations which yielded significant results were the electroencephalograms. In Cases 2 and 4, E.E.G.s were only done long after one of these acute episodes and were reported to be within normal limits. In Case 3 the E.E.G. during her last febrile episode was grossly abnormal, suggesting damage to the midbrain. Five months later, however, concurrent with much clinical improvement, her E.E.G. had almost returned to normal. In Case 5 the E.E.G., during her acute illness in 1954, showed exactly the same abnormalities as in Case 3. Six months later, after much clinical improvement, her E.E.G. became normal. Other investigations (liver function tests, urinary amino-acid chromatograms, C.S.F., Wassermann reaction, air encephalography and toxoplasmosis tests) were all non-contributory in those children in whom they were performed.

The mother had three other pregnancies during her second marriage. A boy, born two years after Case 4, on July 8, 1948, was first seen in the group examined on December 8, 1948, when he appeared to be a healthy, bottle-fed baby. He later began walking and talking at the average age. No abnormalities were detected when 3, 4 and 5 years of age, and he entered school normally when 5 years old. During the third acute family illness, in April, 1954, he became ill with a cold and fever, shortly after his two sisters, Cases 3 and 5, and his brother, Case 4. He was admitted to the Sheffield Children's Hospital. No neurological abnormalities were found; an electroencephalogram was normal and he made a rapid recovery. He appeared to be a healthy, normal child at re-examination in August, 1954.

The mother next had a still-birth in 1950, and then a premature boy weighing 4 lb. 15 oz., delivered by Caesarean section on February 25, 1951. This baby died at home at the age of 11 weeks, on May 10, 1951, from 'pneumonia', of which we have no details.

Discussion

The histories of our patients are, through domestic circumstances, not as complete as we would have liked.

It seems to us that the illnesses of our patients can be divided into two stages: (1) An underlying heredo-familial neurological disorder affecting the father and at least five children; (2) superadded acute episodes with unconsciousness.

The nature of these acute episodes is a matter of speculation. We did not see any of the children during their acute illness in 1948, nor do we know if any earlier episodes occurred. During the episodes that we observed in 1954 the early symptoms and signs were very suggestive of the prodromal stage of measles, but it appears likely that the illnesses in 1948 and 1953 were of a similar nature and were not in fact measles. In 1948, however, the children were reported to have had a rash, but no rash was present in the more recent episodes. The severe disturbance of consciousness which lasted for several months in one surviving child, and the type of neurological residua, are unlike those of measles encephalitis. It is possible that these episodes were acute exacerbations of a demyelinating process. It is perhaps more likely, however, in view of the apparent infectivity of the illnesses, since several children were affected at the same time, that they were attacks of encephalomyelitis, possibly of virus origin, superimposed upon an already abnormal and unusually susceptible nervous system. A virus might cause this disturbance either by direct invasion of the nervous system or by an allergic or anaphylactoid reaction, such as that which may be responsible for the post-infective encephalitides (Ferraro, 1944). The absence of a pleocytosis in the cerebrospinal fluid of Cases 3 and 5 during the acute stage would seem to make a direct viral invasion less likely. This hypothesis might explain why the normal child, born in 1948, without the basic heredofamilial nervous disorder, did not develop neurological sequelae in the 1954 illness. As the nervous system was not examined at necropsy in our one fatal case (Case 1) the above explanation is pure conjecture.

The gross abnormality of the E.E.G.s in an acute phase of the illness in Cases 3 and 5, the subsequent return of the E.E.G.s to approximately normal after recovery, and the normal E.E.G.s after the acute stage in Cases 2 and 4 suggest that the acute febrile episodes were affections of the brain, and not non-specific infections which led to clinical deterioration merely by their debilitating effect.

According to Miller and Evans (1953) recurrence of post-infective acute disseminated encephalomyelitis is almost unknown, and in the rare instances of recurrence it may follow other exanthems or minor non-specific infections, usually of the upper respiratory tract, as a result of which

lasting immunity does not develop. Miller and Gibbons (1954) described recurring encephalomyelitis in three children in the same family, most of the episodes being precipitated by upper respiratory infections. One of the children, a boy of 14, had as many as six encephalitic episodes during a period of eight months. All three children, however, unlike our cases, were eventually left free of neurological sequelae. These authors postulated an anaphylactoid hypersensitivity to an infecting virus in the upper respiratory tract as the cause of their neurological episodes, and the fact that several of the episodes responded to A.C.T.H. supported their hypothesis.

Hepato-lenticular degeneration may affect several siblings and its course may be punctuated with episodes of coma. The points against such a diagnosis in our cases were that the father was also similarly affected, that no cirrhosis of the liver was noted at necropsy of Case 1, that no abnormal amino-aciduria was demonstrated in two of our cases (Nos. 2 and 5), that the liver function tests were normal in all four living children, that none of our cases had Kayser-Fleischer rings, and finally, the prolonged course of the disease.

Tinel and Badonnel (1934) reported two brothers in a family of three children with normal parents, who, after normal development until 14 months of age, both developed, at the same chronological age but not simultaneously, a neurological illness. The first child had convulsions, and this was followed four months later by blindness and optic atrophy. At 2½ years of age he had measles or German measles with subsequent wasting of the limbs, inability to walk, equinus deformity of the feet, scanning speech, horizontal nystagmus, and intention tremor. He became an idiot with spastic paraplegia and absent ankle jerks. The cerebrospinal fluid was normal at an unspecified stage of the disease. The second child was normal until 14 months and then developed vertical nystagmus. At 18 months he had fairly severe measles or German measles, and this was followed by rapidly progressive blindness, wasting of the legs and increasing mental retardation. The cerebrospinal fluid was normal. The final outcome was similar to that of his elder brother, namely, idiocy, spastic paraplegia, cerebellar syndrome, wasting of the muscles of the lower limbs, with absent ankle jerks, and blindness. The history of these two children is somewhat similar to our cases, but the neurological syndrome is quite unlike that which developed in our patients.

Summary

A new heredo-familial neurological disorder affecting a father and five of his children is described with detailed case histories of each. The main features of the condition consisted of athetosis, hypotonia, absent tendon reflexes, extensor plantar responses, mental retardation and periodic febrile attacks occurring in several members of the family with episodes of prolonged unconsciousness.

The possible aetiology of the condition is discussed, and familial recurrent encephalitic illnesses reported in the literature have been reviewed.

We thank Professor R. S. Illingworth and Dr. T. Colver for permission to study their cases; Professor R. S. Illingworth and Sir Charles Symonds for their helpful criticism; Dr. C. E. Dent and Dr. H. Bickel for the amino-acid chromatograms; Dr. J. W. Warboys for the electro-encephalograms; Professor C. P. Beattie and Dr. J. K. A. Beverley for serological tests; Mr. G. P. Elphick for examining the eyes of Case 2, and Dr. T. E. D. Beavan for his permission to use the notes of his examination of Cases 1 and 2 before they came under our observation; and Dr. J. Main Russell who, as Divisional Medical Officer of Health, afforded us many contacts with the family.

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THE CORRELATION OF CLINICAL AND BACTERIOLOGICAL FINDINGS IN INFANTILE GASTRO-ENTERITIS

BY

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During the two years from March, 1950, to March, 1952, a working party established by the Antibiotics Clinical Trials (Non-tuberculous Conditions) Committee of the Medical Research Council investigated the clinical effects of chloramphenicol, aureomycin and sulphadiazine on infants suffering from gastro-enteritis (Medical Research Council, 1953). One of the 10 centres taking part was at Alder Hey Children's Hospital, Liverpool, and at this centre two wards in the University Department of Child Health, each comprising 14 single cubicles, were used for the investigation. In addition to the clinical observations, particular attention was paid to certain bacteriological aspects and especially to the frequency with which *Bact. coli* Types O III and O 55 were isolated from the stools. It is the purpose of this paper to correlate the clinical and bacteriological findings encountered during this investigation.

The design of the trial was described in the report cited above; we therefore propose to give in this paper only those details which are relevant to the clinical and bacteriological aspects of gastro-enteritis under discussion. The infants were assessed on admission with regard to severity and placed into 'mild' and 'severe' groups. In the latter group the infants were sufficiently dehydrated to require immediate intravenous fluid therapy, whereas in the former group parenteral fluids were not given. 'Mild' and 'severe' groups were subdivided into three age groups: under 1 month, 1 to 5 months, 6 to 11 months, and infants admitted into each of these categories were allocated alternately to 'routine' and 'treatment' groups. The 'routine' therapy was that which had been in use at the hospital for the preceding two years and consisted in offering to the 'mild' cases a glucose and electrolyte solution by mouth in a volume of 2½ oz. per lb. during the first 24 hours and then offering milk in increasing strength until 50 calories per lb. were being taken after seven days. The 'severe' cases were given intravenous glucose and electrolytes for 24 hours and then the same treatment as the 'mild' cases. In a majority of the cases receiving routine treatment, chemotherapeutic agents were not given, but one of the patients received oral sulphamezathine because he developed conjunctivitis, and 12 patients were given penicillin intramuscularly and three streptomycin intramuscularly because they developed pyogenic infections such as nasopharyngitis, otitis media, bronchitis or drip sepsis. Patients in the 'treatment' group received the same glucose and electrolyte therapy as the 'routine' group and they were also given chloramphenicol or aureomycin or sulphadiazine orally for seven days from the date of admission to the investigation. The dosage of chloramphenicol and aureomycin was 75 mg. per lb. per day, and of sulphadiazine 125 mg. per lb. per day.

The two-year period of study fell into three phases: phase 1 from March to October, 1950, when the 'treatment' group received chloramphenicol, phase 2 from November, 1950, to May, 1951, when there were two 'treatment' groups receiving chloramphenicol and aureomycin respectively, and phase 3 from June, 1951, to March, 1952, when chloramphenicol or sulphadiazine was given to the 'treatment' groups.

Bacteriological studies were made with special reference to the presence of certain serologically identifiable types of *Bact. coli*. Rectal swabs were taken by specially trained nursing staffs immediately the infant was admitted to the ward and were examined by techniques similar to those described in a previous publication (Kirby, Hall and Coackley, 1950). Patients found to have either shigella or salmonella infections were excluded from the study. Further rectal swabs were taken on the second,

fourth, sixth, ninth and thirteenth days after admission and subsequently at four-day intervals until discharge. In the first phase of the investigation sera for the identification of *Bact. coli.* Types O III and O 55 were used. Sera for the identification of *Bact. coli.* Types O 26, O 86, and E 611 were subsequently received from Dr. Joan Taylor and were used in the second and third phases. As most of the other centres cooperating in the M.R.C. investigation were using only the sera for identification of *Bact. coli.* Types O III and O 55, the bacteriological data in that report (Medical Research Council, 1953) refer to these two serotypes of *Bact. coli.* We thought it best to retain the same criteria, and cases from which either *Bact. coli* Type O III or Type O 55 was isolated are referred to below as 'positive'. The 'negative' group therefore includes cases in which other serologically identifiable types of *Bact. coli* might have been present. That this number is probably small is suggested by the results obtained during the second and third phases of the investigation when additional sera were used, only five strains other than *Bact. coli* Types O III and O 55 being isolated during this period.

Results

Distribution of Cases by Clinical Criteria. Two hundred and fifteen infants were studied during the two-year period; 149 of these fell into the mild and 66 into the severe groups. This total of 215 includes seven additional patients not included in the M.R.C. working party report; they were studied in the short intervals which occurred between the three phases of the investigation when the arrangements for the subsequent stages were being discussed, and they are included in the present report which covers all patients admitted to the gastro-enteritis unit during the two-year period.

Table 1 shows the distribution of the 215 cases into the various sub-groups according to severity, age and treatment. The age-group 1 to 5 months provided the largest number of patients and comprised 75% of the total. The proportion of mild to severe in the whole series was 2·25 to 1 and in the individual phases was 2·85 to 1, 1·54 to 1 and 2·48 to 1 respectively. Although in phase 2 the proportion of severe cases was higher, there is no significant trend of change in severity throughout the period of investigation. As to treatment, in the first phase 41 infants received routine therapy and 40 were given chloramphenicol in addition; in the second phase 21 infants were given routine therapy, 20 received chloramphenicol and 20 aureomycin; in phase 3 there were 26 infants in the routine group, 25 received chloramphenicol and 22 sulphadiazine.

Distribution of Cases by Bacteriological Criteria. In Table 2 the cases are grouped within the severity, age and treatment sub-divisions as 'positive' or 'negative' according to the results of examination of the admission swab for *Bact. coli* Types O III and O 55. Table 2 shows that within the larger mild and severe groups, positive and negative cases were distributed fairly evenly between the various treatment sub-groups. The most important observation is with regard to the incidence of specific types of *Bact. coli* in the mild and severe groups as a whole. Among 149 clinically mild cases in all age groups 62 (42%) were bacteriologically positive, and in the severe group 43 out of 66 cases (65%) were positive.

TABLE 1
SEVERITY, AGE AND TREATMENT GROUPS

Mild Cases Age Group	Under 1 Month			1 to 5 months			6 to 11 months			Totals
Phase of Investigation	1	2	3	1	2	3	1	2	3	
Treatment Groups: Routine	3	0	1	21	11	13	7	2	4	62
Chloramphenicol	3	0	1	20	10	13	6	2	4	59
Aureomycin	—	—	—	—	11	—	—	1	—	12
Sulphadiazine	—	—	—	—	—	13	—	—	3	16
Totals	6	0	2	41	32	39	13	5	11	149

Severe Cases Age Group	Under 1 Month			1 to 5 months			6 to 11 months			Totals
Phase of Investigation	1	2	3	1	2	3	1	2	3	
Treatment Groups: Routine	—	1	1	9	5	5	1	2	2	26
Chloramphenicol	—	—	—	10	5	5	1	3	2	26
Aureomycin	—	—	—	—	5	—	—	3	—	8
Sulphadiazine	—	—	—	—	—	5	—	—	1	6
Totals	0	1	1	19	15	15	2	8	5	66

This is a significant difference ($\chi^2=9{\cdot}25n=1$, P less than 0·01).

Correlation of Symptoms before Admission with Bacteriological Findings on Admission. It is sometimes possible to study the clinical features of infants in whom specific types of *Bact. coli* are present in the stools before they show evidence of gastro-enteritis. In such infants loss of weight and anorexia may be important features (Todd and Hall, 1953). In the 215 cases under discussion weight records indicating their progress before admission to hospital

TABLE 2
BACTERIOLOGICAL DIVISION OF SEVERITY, AGE AND TREATMENT GROUPS

Severity		Mild				Severe				Totals (Mild and Severe)
Age Group		Under 1 Month	1 to 5 Months	6 to 11 Months	All Age Groups	Under 1 Month	1 to 5 Months	6 to 11 Months	All Age Groups	
Routine	—Negative	2	24	11	37	—	9	2	11	48
	—Positive	2	21	2	25	2	10	3	15	40
Chloramphenicol	—Negative	2	23	8	33	—	6	2	8	41
	—Positive	2	20	4	26	—	14	4	18	44
Aureomycin	—Negative	—	5	1	6	—	1	2	3	12
	—Positive	—	6	—	6	—	4	1	5	10
Sulphadiazine	—Negative	—	9	2	11	—	1	—	1	9
	—Positive	—	4	1	5	—	4	1	5	11
Totals	—Negative	4	61	22	87	—	17	6	23	110
	—Positive	4	51	7	62	2	32	9	43	105
Totals		8	112	29	149	2	49	15	66	215

In 'positive' cases a specific *Bact. coli* serotype was isolated on admission and in 'negative' cases no specific *Bact. coli* serotypes were isolated on admission.

TABLE 3A
AVERAGE DURATION OF SYMPTOMS BEFORE ADMISSION

Treatment Group	Negative				Positive			
	Number of Cases	Average Duration in Days			Number of Cases	Average Duration in Days		
		Anorexia	Vomiting	Diarrhoea		Anorexia	Vomiting	Diarrhoea
Mild								
Routine	37	1·9	2·8	2·8	25	0·7	2·6	3·1
Chloramphenicol	33	1·0	4·1	3·1	26	1·1	2·8	3·6
Aureomycin	6	0·3	3·5	3·8	6	1·1	1·0	2·0
Sulphadiazine	11	0·3	5·0	5·9	5	1·4	3·6	4·0
Total	87	1·0	3·5	3·3	62	1·0	3·0	3·3
Severe								
Routine	11	2·0	1·6	1·9	15	1·6	3·8	4·2
Chloramphenicol	8	0·2	1·5	2·1	18	1·1	2·3	4·0
Aureomycin	3	0	6·3	7·0	5	2·4	2·8	3·4
Sulphadiazine	1	4·0	0	4·0	5	1·0	2·0	3·2
Total	23	1·2	2·1	2·7	43	1·4	2·9	3·9

TABLE 3B
AVERAGE DURATION OF SYMPTOMS AFTER ADMISSION (EXCLUDING SIX DEATHS)

Treatment Group	Negative					Positive				
	Number of Cases	Average Duration in Days			Days to Clinical Recovery	Number of Cases	Average Duration in Days			Days to Clinical Recovery
		Anorexia	Vomiting	Diarrhoea			Anorexia	Vomiting	Diarrhoea	
Mild										
Routine	37	3·7	4·4	8·6	13·6	23	4·0	3·8	12·5	21·0
Chloramphenicol	32	1·3	1·9	6·7	10·7	26	1·2	1·2	4·9	10·3
Aureomycin	6	0	1·5	9·8	14·0	6	0·8	1·5	4·8	10·5
Sulphadiazine	11	0·2	0·7	4·0	6·5	5	0·6	1·8	11·8	15·0
Total	86	2·1	2·8	7·4	11·6	60	2·2	2·3	8·4	14·6
Severe										
Routine	11	2·0	0·5	8·8	12·0	13	8·0	3·6	12·1	19·8
Chloramphenicol	8	0·5	0·1	5·1	8·2	18	1·9	2·5	6·6	12·5
Aureomycin	3	0	1·6	8	11·3	5	0·8	0·8	5·2	9·8
Sulphadiazine	—	—	—	—	—	5	0·6	0·6	5·0	7·8
Total	22	1·1	0·5	7·3	10·5	41	3·5	2·4	8·0	13·9

were not available, and in many cases the detailed history of the illness before the onset of diarrhoea and vomiting was unreliable. An attempt has been made, however, to compare the clinical features before admission of those patients who were bacteriologically positive on admission with those bacteriologically negative (Table 3A). Among the mild cases, the duration of anorexia, vomiting and diarrhoea before admission was the same in the bacteriologically negative and positive groups. In the severe cases the duration of anorexia and vomiting was similar in the two bacteriological groups, but the diarrhoea was of longer duration (3·9 days against 2·7 days) in the bacteriologically positive cases. Formerly it was often possible on clinical grounds to suspect the presence of specific types of *Bact. coli*, but in this series of cases there was no clear-cut clinical picture which would enable the clinician to distinguish bacteriologically negative from positive cases.

Correlation of Symptoms after Admission with Bacteriological Findings on Admission and with Treatment. In Table 3B are assembled the data with regard to the duration of anorexia, vomiting, diarrhoea and days to clinical recovery in the various sub-groups for patients who recovered. The numbers in the aureomycin and sulphadiazine groups are small, and will not permit detailed analysis but it was our impression that these drugs had a beneficial action similar to that of chloramphenicol. Certain trends are apparent in the routine and chloramphenicol groups. There is a tendency for recovery, as judged by the above criteria, to take longer in the routine mild and severe positive groups than in the corresponding negative groups; in the chloramphenicol series this difference is less marked in the severe cases, and does not appear at all in the mild cases. Furthermore, the differences in rates of recovery between corresponding chloramphenicol and routine sub-groups are greater in the positive than in the negative cases.

As the time to clinical recovery was considered the most satisfactory criterion of cure, the figures for this assessment have been analysed statistically. The relevant data are given in Table 4. The final column

TABLE 4

STATISTICAL ANALYSIS OF DAYS TO RECOVERY OF CASES IN THE VARIOUS SUB-GROUPS

A

Clinical and Bacteriological Sub-groups			No. of Cases	Mean Days to Recovery	Variance of Mean
Mild	Routine	Negative	37	13·6	3·083
	Routine	Positive	23	21·0	3·514
	Chloramphenicol	Negative	32	10·7	1·292
	Chloramphenicol	Positive	26	10·3	0·755
Severe	Routine	Negative	11	12·0	2·31
	Routine	Positive	13	19·8	10·83
	Chloramphenicol	Negative	8	8·2	0·536
	Chloramphenicol	Positive	18	12·5	1·036

B

Severity (1)	Sub-groups Compared (2)	Difference of Means (3)	Standard Error of Difference of Means (4)	Ratio of (3) to (4)
Mild	Routine Negative v. Routine Positive	7·4	2·568	2·88
	Chloramphenicol Negative v. Chloramphenicol Positive	0·4	1·43	0·28
	Routine Negative v. Chloramphenicol Negative	2·9	2·09	1·38
	Routine Positive v. Chloramphenicol Positive	10·7	2·06	5·2
Severe	Routine Negative v. Routine Positive	7·8	3·62	2·16
	Chloramphenicol Negative v. Chloramphenicol Positive	4·3	1·25	3·44
	Routine Negative v. Chloramphenicol Negative	3·8	1·68	2·26
	Routine Positive v. Chloramphenicol Positive	7·3	3·44	2·12

TABLE 5

NUMBER OF MILD CASES BECOMING SEVERE AND SEVERE CASES REQUIRING FURTHER INTRAVENOUS THERAPY (EXCLUDING DEATHS)

	Negative		Positive	
	Mild → Severe	Severe → Further Intravenous Therapy	Mild → Severe	Severe → Further Intravenous Therapy
Mild				
Routine	6/37	—	15/23	—
Chloramphenicol	1/32	—	2/26	—
Aureomycin	0/6	—	2/6	—
Sulphadiazine	0/11	—	1/5	—
Severe				
Routine	—	0/11	—	9/13
Chloramphenicol	—	0/8	—	0/18
Aureomycin	—	0/3	—	1/5
Sulphadiazine	—	—	—	0/5
	7/86	0/22	20/60	10/41
Totals	7/108		30/101	

in Table 4B gives the ratio, for pairs of corresponding groups, of the differences of means to the standard errors of these differences. Adopting a significance level of 2 for this ratio, several conclusions may be drawn.

Considering first the mild cases, in which the numbers in each sub-group are considerable, there is a significant difference in the rate of recovery between those cases initially positive and those initially negative when routine treatment only is employed. The negative cases respond much more satisfactorily. When chloramphenicol is used, however, this difference disappears. Furthermore, though there is a highly significant difference between the positive cases treated with and without chloramphenicol, this difference is not apparent in the comparison of corresponding negative cases. It should be noted at this point that the routine negative group included an appreciable number of initially negative cases which became cross-infected. Though, as will be shown below, these cases followed a course more closely parallel to cases initially positive than to those initially negative, they do not obscure the differences between positive and negative groups.

These conclusions might be presented in non-statistical fashion by saying that positive cases given only routine treatment responded much more slowly than negative ones, but that when chloramphenicol was used there was no difference in the rates of recovery between the two groups. Chloramphenicol had little, if any, effect in the treatment of negative cases, but a striking effect in the treatment of positive ones.

Turning now to the severe cases, it must first be pointed out that the numbers in the sub-groups are considerably smaller than in the mild series. There are certain similarities to the mild series; positive cases responded less quickly to routine treatment than did negative ones, and chloramphenicol was more effective than routine treatment in positive cases. In contrast to the mild series, chloramphenicol appeared to have some effect in the treatment of negative cases; this difference, however, might have been less apparent, or perhaps absent, if the routine negative series had not included a disproportionate number of cross-infected cases in which the time to recovery was greater than the average. Finally, again in contrast to the mild series, the rate of recovery of positive cases given chloramphenicol did not match that of the eight cases in the corresponding negative group.

A full analysis of the data relating to diarrhoea was also made. There was no significant difference between the corresponding positive and negative groups, but there was a significantly shorter period of diarrhoea in both mild and severe chloramphenicol-treated groups, as compared with the corresponding routine groups.

Delayed Progress. From the clinical point of view many of the patients responded satisfactorily but in some of them the symptoms of gastro-enteritis became more severe during the period of observation and treatment. This delay in recovery occurred both in respect of the number of mild cases subsequently requiring intravenous therapy and also in the number of severe cases needing additional intravenous therapy. Table 5 shows that among 108 bacteriologically negative patients who survived there were seven such infants, and that among 101 surviving bacteriologically positive cases there were 30. These differences are statistically significant and show that patients bacteriologically positive are more

likely to suffer relapses and delayed progress than are the negative cases. As will be mentioned later, of the seven negative cases showing delayed progress, three were cross-infected with specific types of *Bact. coli*.

Deaths. There were six deaths among the 215 cases. Two of the patients were in the routine mild positive group: one of these died suddenly on the sixth day and necropsy revealed that death was due to inhalation of vomit and the other died suddenly on the ninth day but no obvious cause for death was found at necropsy. Two deaths occurred in the routine severe positive group, one on the eleventh day from aspiration of vomit, and the other on the thirty-first day from meningitis due to *Bact. coli* Type O III. There was one sudden death in the mild chloramphenicol negative group, no obvious cause of death being found at necropsy, but *Bact. coli* Type O 86 was isolated from the stools. One patient died on the day after admission and at necropsy there was early haemorrhagic peritonitis. This patient was in the severe, negative, sulphadiazine group.

In the M.R.C. report a further death is recorded in the Liverpool series. This patient was admitted with diarrhoea and vomiting and was in the routine severe negative group. She died on the sixth day following an operation for intussusception. We have excluded this case from the present series because we feel that the diagnosis on admission was incorrectly made in view of the subsequent clinical findings.

Although this small number of deaths does not enable us to draw any firm conclusions about the possible value of the treatment they had received, it is perhaps worthy of note that excluding the patient who died within 24 hours of admission, four of the five deaths were in the routine positive groups and the fifth was infected with *Bact. coli* Type O 86.

Effect of Treatment on Bacteriological Flora of Stools. The bacteriological data so far considered relate only to the incidence of specific types of *Bact. coli* on admission to the investigation. Subsequent examinations enabled us to form some impressions of the effect of treatment on the *Bact. coli* flora as a whole, and on the persistence of specific types of *Bact. coli* during the course of the disease.

The MacConkey plate cultures of all rectal swabs were assessed as showing profuse, moderate, scanty or no growth of *Bact. coli*. When specific types of *Bact. coli* were identified, a similar assessment was made of the frequency of colonies of the specific strain in relation to the total number of *Bact. coli* colonies. It is obvious that such observations were crude, and might have been influenced by a number of extraneous factors; nevertheless certain trends are apparent.

Table 6 shows the frequency with which a scanty growth of *Bact. coli*, or no growth at all, occurred at comparable times during treatment in the routine mild and chloramphenicol mild groups. It can be seen that there was little variation from day to day in the routine group, but that chloramphenicol had, during the seven days of treatment, a mild suppressive action on the total *Bact. coli* flora. This effect rapidly disappeared after cessation of treatment. Further investigations showed that this suppressive effect was not due to carry-over of antibiotic from the rectal swab directly affecting the appearance of *Bact. coli* colonies on the plate. Similar results were obtained in the smaller severe routine and chloramphenicol groups, and in the series treated with aureomycin and sulphadiazine.

Table 7 shows similar data relating to the presence of specific types of *Bact. coli*. In the routine mild positive group specific strains began to disappear about a fortnight after treatment was started, but in the chloramphenicol mild positive group this effect was observed much earlier. Owing to the early discharge of clinically well cases in this latter group, we were unable to follow all of them bacteriologically for a sufficient time, but it was apparent from those in which data were more adequate that this

TABLE 6
EFFECT OF TREATMENT ON *BACT. COLI* FLORA

Treatment Group	Total No. of Swabs	Days Swabs Taken					
		0–1	2–3	4–5	6–8	9–12	13–14
Routine mild positive and negative	(*a*) Taken	60	52	52	58	55	42
	(*b*) Showing scanty or no growth	8	7	5	3	5	6
Chloramphenicol mild positive and negative	(*a*) Taken	58	53	54	54	56	35
	(*b*) Showing scanty or no growth	9	10	17	14	7	6

TABLE 7
EFFECT OF TREATMENT ON SPECIFIC SEROTYPES OF *BACT. COLI*

Treatment Group	Total No. of Swabs	Days Swabs Taken					
		0–1	2–3	4–5	6–8	9–12	13–14
Routine Mild Positive	(*a*) Taken	25	23	23	22	21	21
	(*b*) Showing no growth of specific serotypes	0	3	3	3	3	10
Chloramphenicol Mild Positive	(*a*) as above	26	25	23	26	26	16
	(*b*) as above	0	3	9	20	21	10
Routine Severe Positive	(*a*) as above	14	13	12	13	13	13
	(*b*) as above	0	0	1	2	5	8
Chloramphenicol Severe Positive	(*a*) as above	18	18	17	18	18	18
	(*b*) as above	0	3	8	13	15	11

early suppression of specific types of *Bact. coli* was not infrequently followed by their reappearance or increase in numbers a few days after the cessation of chloramphenicol treatment. In spite of this, however, clinical improvement was generally uninterrupted.

In the routine mild positive group, because of the more protracted clinical course, additional data regarding clearance of specific strains were obtained, the criterion of clearance being three consecutive negative swabs at four-day intervals. Of 20 patients remaining in hospital beyond the fourteenth day, and from whom adequate numbers of swabs were obtained, 11 had become negative by the fourteenth day, a further six remained positive for periods ranging from 17 to 42 days from admission, and three were still positive on discharge at 22, 30 and 37 days. In the chloramphenicol mild group, and because of more rapid recovery and discharge, there were only seven comparable cases, of which four had become negative by the fourteenth day. Two remained negative after the seventeenth and nineteenth days, respectively, and the other was discharged positive on the twenty-fifth day.

The lower half of Table 7 shows that in the chloramphenicol severe positive group there was an early suppression of specific types of *Bact. coli* similar to that observed in the corresponding mild series.

Of 10 patients in the routine severe positive group, followed adequately beyond the fourteenth day, five remained negative after that day, four remained positive from 20 to 34 days, and one died, still positive, on the thirty-first day. In the chloramphenicol severe group, of 11 patients available, six remained negative after the fourteenth day, the others becoming negative between the seventeenth and twenty-ninth days. Similar trends were observed in the smaller series treated with aureomycin and sulphadiazine.

Effect of Cross-infection. In spite of close attention to details of isolation technique, cross-infection by serologically identifiable types of *Bact. coli* was occasionally observed. In the positive group its frequency and significance could not be ascertained. As 91 of the 115 cases in this group were initially infected with *Bact. coli* Type O III, cross-infection by this organism within the group would remain undetected. Even in those instances where a positive swab was obtained after a short series of negatives, either bacteriological relapse or cross-infection might have occurred. Had we been able to employ H antigen determinations, it might have been possible to detect some instances of cross-infection but others would have passed unnoticed. In one instance cross-infection by *Bact. coli* Type O III of a case initially infected with *Bact. coli* Type O 55 was noted.

In the negative group, however, cross-infection could be followed more easily. Of the 110 cases, 12 became cross-infected during the first fortnight, two in the routine severe group and seven in the routine mild group. Cross-infection in this latter group was associated with retardation of clinical progress; of a total of 37 mild routine negative cases six became severe (Table 4); three of these were cross-infected. The period to clinical recovery and duration of diarrhoea tended to be prolonged. Comparing the seven cross-infected with the 30 non-cross-infected cases in the routine mild group, with reference to days to recovery and duration of diarrhoea, the difference of means were respectively 2·4 and 3·3 times their standard errors.

With routine treatment only, therefore, the response of the cross-infected cases paralleled that

of the cases initially positive rather than that of those always negative.

Sensitivity of *Bact. coli* to Drugs Used. In almost all cases studied, the specific types of *Bact. coli* were tested for sensitivity when first isolated and on subsequent isolations. In all instances in the chloramphenicol groups the organism was sensitive to 10 mg./ml. or less of chloramphenicol included in agar slopes, and in only one case did a significant degree of resistance develop during treatment. In the much smaller aureomycin and sulphadiazine series similar results were obtained.

Discussion

The term infantile gastro-enteritis is usually applied to an illness affecting infants under the age of 1 year and it is characterized by diarrhoea and often by vomiting and dehydration. Such a clinical picture may result from infection by salmonella and dysentery organisms, and some investigators have thought that *Proteus vulgaris* and virus infections may also produce a similar clinical picture. It is therefore not surprising that response to specific chemotherapeutic drugs should vary in different epidemics of gastro-enteritis, especially when clinical criteria alone are used and bacteriological studies not undertaken. Since 1945 there has been increasing evidence that one form of gastro-enteritis is caused by specific serotypes of *Bact. coli* and in the present series of 215 patients we have paid particular attention to the presence of these types.

Holzel, Martyn and Apter (1949) studied 79 patients in Manchester with diarrhoea and vomiting and found that a specific type of *Bact. coli* was present more often in the stools of severely ill patients than in those with moderate or mild symptoms. In addition, the mortality rate in patients from whom this type was isolated was significantly higher than in those without specific organisms. Taylor, Powell and Wright (1949) found that in London and other centres in England the great majority of babies from whom *Bact. coli* Type O III was isolated had a severe form of gastro-enteritis with dehydration of such a degree that intravenous infusion was required, and that recurrence of symptoms in patients who did not excrete this serotype on admission was associated with the isolation of this organism when the symptoms recurred. Shanks and Studzinski (1952) also found in Glasgow that there was a tendency for milder cases to be less often associated with specific serotypes of *Bact. coli* and that the organisms appeared simultaneously with a clinical relapse. Alexander, Benjamin, Maslen and Roden 1952) studied infantile gastro-enteritis at St. Ann's General Hospital, London, and found that the percentage of cases from which specific serotypes of *Bact. coli* were isolated increased with increasing severity of symptoms. In a similar study in Finland, Rantasalo and Hallman (1953) found that specific serotypes of *Bact. coli* were more frequently found in the severe 'toxic' cases of gastro-enteritis than in the mild cases. The present series shows similar trends in that 62 (42%) of 149 clinically mild cases were infected with two serotypes of *Bact. coli* compared with 43 (65%) of 66 clinically severe cases, and that three of the seven infants among the 108 bacteriologically negative on admission in whom progress was delayed were cross-infected with a specific type of *Bact. coli*. Furthermore, among the 101 bacteriologically positive patients who survived there were 30 in whom progress was delayed. Taking the mild cases which received no specific chemotherapy, it was found that six of the 37 patients in the mild negative group became severe during observation, whereas 15 of the 23 patients in the mild positive group became severe. None of the 11 patients in the routine severe negative group required further intravenous therapy, whereas nine of the 13 patients in the routine positive group needed further intravenous fluids. These findings are statistically significant and show that patients from whom specific types of *Bact. coli* were isolated were more liable to have severe symptoms and their clinical progress was more likely to be delayed than those patients from whom specific types of *Bact. coli* were not isolated.

The effect of specific chemotherapy on the course of the disease in the negative and positive cases is worthy of note. Since the patients who received aureomycin or sulphadiazine were relatively few in number, and those given chloramphenicol comprised the largest group receiving chemotherapy, only the latter will be considered in comparing the progress of positive and negative cases. In the negative mild group (Table 3B) the average duration of diarrhoea and average number of days to clinical recovery, although slightly less in the chloramphenicol-treated patients, did not differ significantly from the routinely treated patients; but in the mild positive groups there was a marked difference between the routinely and chloramphenicol-treated patients, the days to clinical recovery being almost halved in the patients receiving chloramphenicol. This comparison suggests that chloramphenicol is of little value in mild cases of gastro-enteritis unassociated with specific types of *Bact. coli* but that it is of considerable value in patients infected with specific *Bact. coli* types. The number of

severe cases of gastro-enteritis studied was not large but similar trends are apparent. In the severe routine negative cases the days to clinical recovery (12 days) were significantly less than in the severe routine positive cases in which the time to clinical recovery was 19·8 days. There was also a statistically significant reduction from 19·8 to 12·5 days in the days to clinical recovery when comparison is made between the severe routine positive cases and those which received chloramphenicol. Although there was also a statistically significant reduction from 12 to 8·2 days in the severe negative groups, the presence in the routine severe group of two cross-infected cases with periods of recovery considerably above the average suggests that this result should be viewed with caution. These findings suggest that in severe cases of gastro-enteritis unassociated with certain *Bact. coli* serotypes chloramphenicol may be of some value, but that when these organisms are present chloramphenicol is of great benefit as judged by reduction in the duration of diarrhoea and in the days to clinical recovery.

The effect of chloramphenicol upon the bacteriological flora is of interest. This drug had a mild suppressive effect on the specific *Bact. coli* types. The latter effect was often temporary, and the organisms frequently reappeared in the faeces after chloramphenicol had been discontinued. Although there was no recurrence of diarrhoea, the continued excretion of specific *Bact. coli* types in the faeces presented a danger to other infants in the ward and to any young infants who might come in contact with the case after discharge. Our investigations suggest that the organisms may continue to be excreted for some weeks and it would be reasonable to prevent contact with other infants until rectal swabs are negative for specific types of *Bact. coli*. In our experience, such reappearance was not associated with the emergence of resistant strains.

The results of this investigation suggest that in planning therapeutic trials in gastro-enteritis the trial and control groups should be comparable not only with regard to age and severity, but also with regard to the incidence of *Bact. coli* serotypes on admission.

Since this investigation was undertaken, we have encountered strains of *Bact. coli* serotypes which were resistant to chloramphenicol and clinical progress in these cases has not been so satisfactory. Terramycin has proved to be of therapeutic value in cases in which the organisms were shown to be sensitive to this drug.

Summary

Two hundred and fifteen infants suffering from gastro-enteritis have been studied in respect of the clinical features and of the presence of certain types of *Bact. coli*. The clinical and bacteriological response to chloramphenicol, aureomycin and sulphadiazine has also been studied.

Infants from whom *Bact. coli* Types O III and O 55 were isolated usually had more severe symptoms and signs than those from whom no such organisms were isolated. Chloramphenicol appeared to have little influence on the course of the illness in cases unassociated with specific types of *Bact. coli* but was of considerable therapeutic value in patients infected with specific *Bact. coli* types. Chloramphenicol had a mild suppressive action on the total *Bact. coli* flora but a more marked suppressive effect on the specific *Bact. coli* types. Similar clinical and bacteriological features were apparent in patients receiving aureomycin or sulphadiazine. These investigations suggest that in planning therapeutic trials in gastro-enteritis the trial and control groups should be comparable with regard to the incidence of *Bact. coli* serotypes as well as in respect of age and severity.

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FAMILIAL HEPATIC CIRRHOSIS

BY

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Interest has been revived in the aetiology of hepatic fibrosis in infants by the recent communications of Stokes, Berk, Malamut, Drake, Barondess, Bashe, Wolman, Farquhar, Bevan, Drummond, Maycock, Capps and Bennett (1954) and Dible, Hunt, Pugh, Steingold and Wood (1954).

Dible *et al.* showed that hepatitis can occur during intra-uterine life with fatal results in the neonatal period, or perhaps later in infancy and childhood. Their eight cases formed a homogeneous group, with similar histological appearances in the liver, and included siblings.

Stokes *et al.* described a female carrier of an icterogenic virus following homologous serum jaundice, who gave birth to a child who subsequently developed hepatic fibrosis and died at 18 months. They also showed that the plasma of known icterogenic carriers was capable of producing hepatitis in healthy volunteers.

This work has thrown some light on hepatic fibrosis in siblings, and it seems likely that the infants described by Dible *et al.* are only extreme examples, and that many affected infants must survive with some degree of liver damage. However, there is no indication so far as to the cause of this hepatitis; the common virus of infective hepatitis, virus A, does not seem to be involved. The case of Stokes *et al.* indicates that placental transfer of virus can occur, but the frequency of this is not known.

Some cases of hepatic fibrosis in siblings may be due to Rh iso-immunization (Drummond and Watkins, 1946; Craig, 1950), but Gerrard (1952) in a follow-up survey of Rh-affected children could find no evidence of permanent liver damage. A few examples are seen in rare familial states such as Lignac-Fanconi's disease and hepato-lenticular degeneration (Wilson's disease), but the liver damage occurring here is only part of the pathological process, although in Wilson's disease it may be of primary importance.

Cases of hepatic disease in siblings where the aetiology is completely unknown have been called 'familial hepatic cirrhosis' (Weber, 1946).

The family described in this communication is one of seven children; two certainly and most probably a third suffered from severe hepatic disease which caused death in all three before the age of 1 year. An amino-aciduria in certain members of the surviving family is also described.

Case Reports

Case 1. A boy, aged 11 months, was born in December, 1949. He was a normal, full-term baby, was breast fed for two weeks, and then with National dried milk in adequate quantities. No jaundice was seen at, or after birth, and the mother had a normal pregnancy.

The infant was quite well until six days before admission when he began to pass loose, green, offensive stools after every feed. On the day of admission he was found lying in his cot, with legs and arms twitching; apparently consciousness was not lost. On admission he was found to be a well nourished infant, temperature 101° F. (38·3° C.), having continuous generalized convulsions and emitting an occasional high-pitched cry. Apart from a closed anterior fontanelle, no other physical abnormality was found.

Haemoglobin was 89% of normal. A white blood count gave 15,300 (polymorphs 11,500). The Wassermann reaction was negative.

No pathogens were found in the stools.

A blood culture was sterile.

A Mantoux test (1 in 1,000 O.T.) was negative.

The cerebrospinal fluid contained 15 cells per c.mm. and 300 mg. protein.

A radiograph of the skull and chest showed a closed anterior fontanelle, but was otherwise normal.

Bilateral subdural taps revealed no abnormality.

On the assumption that this was an intracranial lesion, the child was transferred to a paediatric unit convenient for a neurosurgeon. Here sedation was gradually withdrawn, and only two further fits were seen until his death. Twitching, mainly left-sided and diaphragmatic, continued and the child was noted to be extremely hypotonic.

Investigation of the cerebrospinal fluid now gave

17 cells (95% lymphocytes), 700 mg. per 100 ml. protein, 102 mg. per 100 ml. sugar. The fluid was sterile on culture.

Further subdural taps and a ventriculogram showed no abnormality. Post-operatively twitching became more pronounced and the child died the following day.

At necropsy the main findings concerned the liver and lungs. The liver (264 g.) showed gross fatty change throughout, the capsule was smooth, and there was a mild cirrhosis. There were areas of haemorrhage on the pleurae and in the lung substance. The brain and spinal cord were normal.

Histologically the liver showed a moderately advanced multilobular cirrhosis with gross fatty change throughout. The fibrous tissue linking the portal tracts was infiltrated by histiocytes and lymphocytes, being especially abundant where necrosis of liver cells was progressing. Much doubly refractile tissue, mainly surrounding the liver cells, was found. Its nature could not be determined in this case. There was little or no proliferation of bile ducts.

The lung showed extensive interstitial haemorrhage. The brain and spinal cord showed no abnormality.

Case 2. A boy, aged 12 months, was born in October, 1952, after a normal full-term delivery. No jaundice at, or after, birth was seen. The baby was bottle fed, and was quite well until the age of 4 months, when he began to have mild attacks of diarrhoea and vomiting; occasionally the stools were grey. The vomiting lasted for 48 hours but recurred at about fortnightly intervals.

When first seen in September, 1953, he weighed 16 lb. 8 oz. and was not obviously ill. He was now passing four or five green-yellow stools daily. Physical examination was negative, but a rectal swab grew *Bact. coli* O 111. Treatment with sulphamezathine lessened the frequency of the stools and the baby was discharged.

When he was admitted one month later, he was passing one hard grey stool daily, was vomiting after each feed, and was reluctant to feed at all.

He was a well nourished child, drowsy and extremely hypotonic, although all reflexes were brisk. Fine twitching of the hands, feet, and face were noted. The liver was just palpable, but no jaundice was seen. The temperature was 100·8° F.

The alkali reserve was 46·6 vol., the blood urea 24 mg. per 100 ml., plasma chlorides 592 mg. per 100 ml., serum calcium 10 mg. per 100 ml., serum potassium 17·8 mg. per 100 ml., serum proteins 6·3 g. per 100 ml. A blood culture was sterile.

The cerebrospinal fluid contained 4 cells per c.mm., 140 mg. protein, 685 mg. chlorides, 80 mg. sugar, 30 mg. urea per 100 ml. Culture was sterile.

A Mantoux test (1 in 1,000 O.T.) was negative.

An air encephalogram showed no abnormality.

The infant was treated with intravenous glucose-saline and aureomycin. Despite a slight initial favourable response the twitching recurred and became more severe. There was little change in biochemistry and the cerebrospinal protein remained high. Gradually he became more drowsy and apparently blind. He died 38 days after admission.

At necropsy the liver weighed 284 g. and was tawny-yellow, with a well marked granular cirrhosis. A few larger hyperplastic nodules of tissue were present in the inner surface. No obstruction to the common duct was seen.

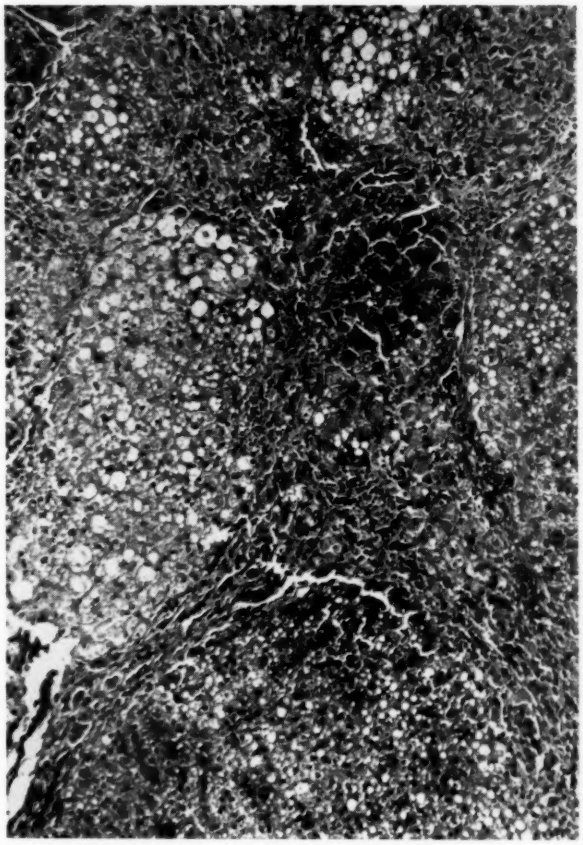

FIG. 1.—Advanced cirrhosis with heavy round cell infiltration of the fibrous tissue bands (H. and E. × 120).

No abnormality was found in the brain, spinal cord, or spleen.

Histologically the liver showed an advanced multilobular cirrhosis (Fig. 1) with gross fatty change in all areas (Fig. 2). There were no apparent normal lobules seen and many of the hyperplastic nodules showed central necrosis and vacuolation. The fibrous tissue bands were heavily infiltrated with histiocytes and round cells, indicating that fibrosis was progressive. There was no conspicuous proliferation of bile ducts. Much doubly refractile tissue was seen by polarized light in frozen sections; much of this was considered to be naturally occurring (Duguid and Mills, 1928). However, some basophilic material, principally between the liver cells, was doubly refractile and appeared pathological,

and seemed to be a fully saturated lipid of the lecithin-cephalin type (Pearse, personal communication). Its presence, even in such quantities, in the liver is of doubtful significance. No abnormal deposition of iron was present.

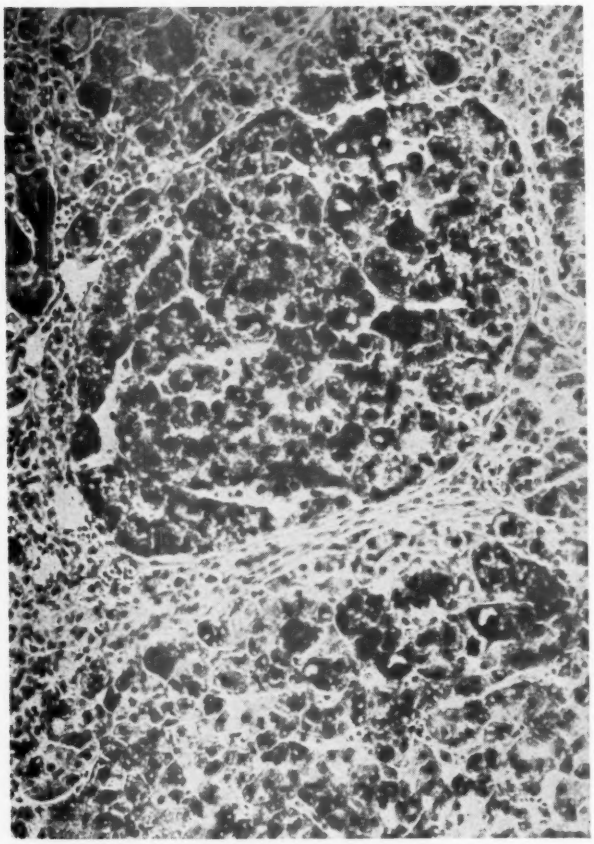

FIG. 2.—A small atypical lobule is shown with gross fatty change in all the cells (fat is shown as black). (Haematoxylin and eosin and Sudan IV × 240.)

Case 3. A boy, aged 12 months, was born in June, 1940. He appeared a normal child, with no jaundice at or after birth. He was bottle fed on Cow and Gate milk. For some two weeks before death, he was fretful with an occasional loose stool. Two days before death, twitching of legs and arms was noted; the child was quite silent now and limp. He began to vomit and to refuse food; the twitching became generalized next day and was followed by repeated convulsions which lasted until death. The family doctor noted moderate jaundice—apparently as a terminal event. The child was not admitted to hospital and no investigations were made.

These infants present a striking clinical picture and the findings at necropsy in two are similar, indicating that the same process was involved in all three. Apart from the liver disease, the only significant finding, the high C.S.F. protein level, remains unexplained. The histological appearances of the brain and spinal cord in two cases were normal.

The parents and one boy and three girls survive. The parents deny consanguinity. The medical histories and physical examinations in all except the boy were negative. In particular, no history of jaundice was obtained, and the mother had never been transfused.

The surviving boy, aged 6 years, was thin, pale and undersized, and addicted to bouts of vomiting, but with a healthy appetite. The only physical finding of note was a palpable liver edge.

Routine liver function tests and stool examinations were carried out and the results are tabulated (Table 1).

In addition, all Wassermann reactions and titres for leptospira were negative. Both parents were Rh positive to anti D. All the children were radiographed, but no bony changes were found. Kayser-Fleischer rings were absent.

From the tables it will be seen that all members of the family have a slightly raised serum bilirubin level, a constant finding on numerous occasions. Two of the girls have an excess of urobilinogen and the boy has a raised alkaline phosphatase. The increased flocculations in all, with normal thymol turbidity readings, is unusual.

A more detailed examination of the urines was made by the cyanide-nitroprusside test for cystine (Brand, Harris and Biloon, 1930) and by two-way partition chromatography (Consden, Gordon and Martin, 1944). These examinations were repeated at monthly intervals and tested for any constancy of pattern. The results are given in Table 2.

The amino-acids, which were in excess of normal in all three, apart from cystine, were glycine, aspartic acid, alanine, taurine, β isoaminobutyric acid and lysine. The father showed an excess of glutamine also. These patterns are difficult to interpret, but, combined with a positive cyanide-nitroprusside reaction for cystine, it

TABLE 1

LABORATORY INVESTIGATIONS IN THE FAMILY

Member of Family	Age	Urine			Alkaline-phosphatase (K/A units)	Thymol Turbidity	Thymol Flocculation Test	Total Serum Bilirubin (mg.)	Serum Inorganic Phosphorus (mg.)	Stool Pathogens Including *Bact. coli*
		Albumin	Sugar	Urobilinogen						
Mother ..	33 years	Trace	Nil	Nil	5	3	1+	1·3	2·6	No pathogens
Father ..	35 ,,	Nil	Nil	Nil	13	2	1+	1·4	—	No pathogens
Girl	7 ,,	Nil	Nil	+	13	2	1+	1·4	4·0	No pathogens
Boy	6 ,,	Nil	Nil	+	18	4	2+	1·5	4·4	No pathogens
Girl	3 ,,	Nil	Nil	Nil	14	1	1+	1·0	4·2	No pathogens
Girl	3 months	Nil	Nil	Nil	12	2	1+	—	—	No pathogens

seems more likely that they represent a progressive hepatic cirrhosis (Walshe, 1953) rather than a familial amino-aciduria as such. Liver biopsy, obviously desirable, could not be performed, so that no definite answer can be given.

TABLE 2

RESULTS OF PARTITION CHROMATOGRAPHY

Member of Family	Cyanide Nitroprusside Test	Chromatogram Results
Father ..	+	Well marked, generalized amino-aciduria, including cystine
Mother ..	−	Amino-acids at the upper limit of normal
Boy .. .. (6 years)	+	Well marked, generalized amino-aciduria, including cystine
Girl .. .. (7 years)	−	Amino-acids at upper limit of normal
Girl .. .. (3 years)	+	Moderate generalized amino-aciduria, including cystine
Girl .. .. (3 months)	−	Probably normal pattern

Urines of close relatives did not show patterns of this order, although investigation was incomplete. The maternal grandmother was found to suffer from cystinuria as defined by Dent and Rose (1951), as also did a maternal uncle. Present evidence (Dent, Heathcote and Joron, 1954) indicates that cystinuria is a condition separate from other amino-acidurias, which breeds true and never has pathological effects outside the urinary system. Since cystinuria is not a very rare disorder (Lewis, 1932), the occurrence in this family may well be coincidental. The indications were that the hepatic cirrhosis and amino-aciduria were confined to the present family. Because of this a search was made for known liver poisons and substances known to cause amino-aciduria, especially lead (Wilson, Thomson and Dent, 1953), but none were found. There was no evidence of malnutrition and living conditions were reasonable.

Discussion

It is useful to compare the hepatic disease in these infants with known causes of infantile cirrhosis.

Intra-uterine Hepatitis (Dible *et al.*, 1954; Craig and Landing, 1952). It would be attractive to consign the cases to this group, but there are several objections. The infants were widely separated in age, the eldest by 13 years and the youngest by three years; none was visibly jaundiced except terminally in one child, and no history of jaundice could be obtained in the rest of the family. The histological pictures, although not irreconcilable, show differences. That seen in the hepatitis group is a more or less acute necrosis with giant cell reaction, iron storage and extra-medullary haemopoiesis. The children in the present series show a multilobular cirrhosis, which, even in the earlier lesion (Case 1), shows no evidence of an acute reaction. It corresponds to the multilobular cirrhosis of insidious onset in adults and differs from this only in the gross fatty change in all areas. However, Craig and Landing showed that neonatal hepatitis could advance to a coarse cirrhosis in time and Dible's cases also indicated that cirrhosis would occur with survival. On histological grounds alone the possibility that the children under discussion suffered from neonatal or intra-uterine hepatitis remains. However, the amino-aciduria exhibited by several surviving members of the family could hardly be entirely explained by a non-icteric hepatitis.

Familial Amino-aciduria. A comparison with the familial amino-acidurias is also useful. There is no evidence that Lignac-Fanconi disease is involved. The absence of glycosuria, bone changes and hyperphosphataemia are conclusive.

The most interesting comparison is with hepato-lenticular degeneration in which multilobular cirrhosis and an amino-aciduria are invariable; the amino-aciduria can be present with histologically normal liver tissue and it can precede neurological signs (Uzman and Denny-Brown, 1948). In 5% of cases the patients die with liver fibrosis before neurological disorders become apparent (André, 1946). However, several factors are against labelling the present children as examples of hepato-lenticular degeneration. No evidence of the disease, especially Kayser-Fleischer rings, is seen in the surviving siblings, and amino-aciduria in the father does not conform to the dictum that the disease is confined to one generation alone.

Other States. There is no evidence that a hepatic virus has been transferred placentally in these children and a carrier state lasting 13 years appears unlikely. Similarly, Rh immunization as a cause is excluded by both parents being Rh positive. There is also no evidence to suggest that the children were suffering from a variant of a known lipoidosis. The lecithin-cephalin in the liver was found in no other organs.

Familial Hepatic Cirrhosis. A review of reports on this group of cases (Weber, 1947; Langmead, 1934; Debré, 1939; Poynton and Wyllie, 1926) shows that they were undoubtedly familial, but the disease was recognized later, in children aged from 5 to 12 years, and usually in the advanced stages of portal hypertension. The cause of death was often ruptured oesophageal varices. The families report-

ed were not investigated for amino-aciduria or Rh antibodies so that comparison is difficult.

Despite this lack, the term "familial hepatic cirrhosis with amino-aciduria" would appear the most appropriate for the family reported now, as the aetiological factors are so far unknown. Liver biopsy, which would be helpful, may be possible if any signs of liver or neurological disease become apparent.

Summary

A family is described of which three children died in early life with hepatic disease. Three remaining members, including the father, show a generalized amino-aciduria and two relatives suffer from cystinuria.

The hepatic fibrosis in the family reported here is compared with other known cases of hepatic fibrosis in childhood, and it is concluded that they fit into no known group. The name "familial hepatic cirrhosis with amino-aciduria" is suggested.

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ERYTHEMA MARGINATUM

BY

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'The signs may be difficult for the physician to interpret and thus cures are slow and mistrust in the power of the doctor persists.'—Hippocrates (translated from the original Greek by John Chadwick and W. N. Mann).

The association of erythematous skin rashes with rheumatic fever was recognized by physicians of the last half century. Perry (1937) reviewed the literature on the subject of erythema marginatum and described 13 cases seen in Bristol over a period of five years. His description of the rash was very similar to that of erythema annulare given by Lehndorff and Leiner in 1922. He wrote that the lesions start as a solid erythema which may be slightly raised. The erythema extends outwards while the skin in the centre returns to normal, hence the name erythema marginatum. Adjacent lesions coalesce, forming larger rings. Keil (1938) studied 523 cases of rheumatic fever admitted to the Mount Sinai Hospital, and in 53 of these an erythematous rash occurred. In 14 this took a papular form, and in 39 a rash with a marginate edge was present. Keil mentioned two variants of this, erythema marginatum and erythema annulare. In the first of these the edge is raised, and in the second the lesions are entirely macular, but the author admitted that it is often difficult to make a clear distinction between the two, as lesions of both types may be seen together and they have a similar distribution, course, duration and diagnostic significance. Jones (1944) stated that in his experience erythema marginatum is by far the most significant cutaneous manifestation of rheumatic fever, and he named it as one of the major criteria for diagnosis of this disease. He did not differentiate erythema marginatum and erythema annulare.

Lehndorff and Leiner considered that erythema annulare was only seen in children with rheumatic carditis. Wallgren (1935) studied 148 children with rheumatic fever, and of these 88 were 'very mild cases of endocarditis which healed relatively rapidly' and only seven had erythema annulare, whereas it was seen in eight of 27 children with very severe rheumatic carditis. In his opinion there is no doubt that erythema annulare occurs more frequently in severe than in mild rheumatic fever. Endocarditis was demonstrated clinically at some time in 17 of 18 children with erythema annulare seen in four years (1931-34). Five of the children died, a fatal outcome was expected in a further three, in three the prognosis was 'doubtful', while in seven it was considered to be good. In contrast, Perry regarded erythema marginatum as of favourable prognostic significance, because five of his 13 patients made a complete recovery, five had permanent cardiac damage, in one the disease was still active and two had died. Keil (1938) came to the conclusion that involvement of the heart 'practically always' accompanies the cutaneous manifestation of rheumatic fever.

Is erythema marginatum a specific rheumatic manifestation? Perry thought it to be so and Lehndorff and Leiner and Wallgren held similar views with reference to the macular form, erythema annulare. These writers noted, however, that the rash may continue to appear when all other signs of rheumatic activity have subsided. Keil was more cautious and said that an eruption may only be regarded as rheumatic in origin in the presence of other manifestations of acute rheumatism. He mentioned drug and serum eruptions in the differential diagnosis, but stated later that in childhood the rash may be regarded as almost certain evidence of acute rheumatism.

The purpose of this paper is to present 19 cases of erythema marginatum, 14 of which were associated with rheumatic fever. Six of the children were included in the joint Anglo-American investigation sponsored by the Medical Research Council, into the use of cortisone, A.C.T.H. and salicylates in rheumatic fever. The 19 children were seen in the Children's Hospital, Sheffield, or The Hospital for Sick Children, Great Ormond Street, London. In this paper no distinction is made between erythema marginatum and erythema annulare and only the term 'erythema marginatum' is used.

TABLE I

SUMMARY OF CASES WITH SPECIAL REFERENCE TO

Case Number	Age in Years	Sex	Disease		Treatment	Duration of Erythema Marginatum	Erythema Marginatum Present before Treatment	Erythema Marginatum Present during Treatment	Erythema Marginatum Present after Treatment Discontinued	E.S.R. (mm./hr.) when Erythema Marginatum Developed	Subsequent Normal E.S.R.s with Erythema Marginatum present	Other Signs of Rheumatic Activity when Erythema Marginatum Developed	Other Signs of Activity Developing Subsequently when Erythema Marginatum present
1	9	M	Rheumatic fever.	A.1	C	18 mth.	+	+	+	40	+	Chorea Nodules	–
2	5	F	Rheumatic fever.	A.3	D		+	+	–	32	–	Nodules	–
				R.1	A	2 yr.	+	+	+	55	–	Arthritis	Nodules
				R.2	A		+	+	+	37	–	Nodules	–
				R.3	A		+	+	+	33	+	—	–
3	12	M	Rheumatic fever.	A.3	D	6 wk.	+	+	–	57	–	Arthritis	–
				R.1	D		+	+	–	19	+	Arthritis	–
4	11	M	Rheumatic fever.	A.2	1. D 2. C	1¼ yr.	+	+		50	+	—	Arthritis
5	9	M	Rheumatic fever.	A.1	D	3 mth.	–	+	+	17	+	Arthritis	Nodules
6	8	M	Rheumatic fever.	A.1	D	2 days	–	+	–	63	–	Arthritis Nodules	Nodules
7	6	M	Rheumatic fever.	A.1	B & D	3 days	–	+	–	68	–	Arthritis	–
				? R.1	—	14 days	+			11	+	—	–
8	13	M	Rheumatic fever.	A.2	D	4 mth.	+	+		63	+	Arthritis	Arthritis
9	9	M	Rheumatic fever.	A.1	B	2½ yr.	+	+	+	39	+	Arthritis Nodules	–
10	12	M	Rheumatic fever.	A.1	A	9 wk.	+	+	+	52	+	Arthritis	–
11	8½	M	Rheumatic fever.	A.2	A	2½ yr.	+	+	+	58	+	Nodules	Nodules
12	9	M	Rheumatic fever.	A.1	B	7 days	+	+	–	54	–	Arthritis	–
				A.2	B	2 ,,	+	+	–	35	–	Arthritis	–
13	7	F	Rheumatic fever.	A.1	B	3 mth.	+	+	+	66	+	Arthritis Nodules	–
14	9	M	Rheumatic fever.	A.1	C	4 mth.	+	+	–	31	+	Arthritis Nodules	Nodules
				A.2	1. C 2. B 3. C	1 yr.	+	+	–	53	+	Arthritis Nodules	Nodules
15	9	M	Bronchiectasis		Penicillin	3 days	–	+	–	N.D.	N.D.	—	–
16	5	F	Nephritis		C	2½ yr.	+	+	+	60	–	—	–
17	7 wk.	M	Diarrhoea		—	5 days	+	–	–	N.D.	–	—	–
18	7	M	Migraine		Phenobarbitone	2 yr.	+	+	+	N.D.	+	—	–
19	3	F	Tonsillitis		D	1 wk.	+	+	–	60	–	—	–

A—signifies attack. R—signifies relapse.

Treatment A. A.C.T.H. as in M.R.C. Trial

80 mg. daily for 4 days.
60 mg. daily for 3 days.
40 mg. daily for 2 weeks.
30 mg. daily for 2 weeks.
20 mg. daily for 1 week.

Treatment B. Cortisone as in M.R.C. Trial

300 mg. first day.
200 mg. daily for 4 days.
100 mg. daily for 16 days.
75 mg. daily for 2 weeks.
50 mg. daily for 1 week.

THE OCCURRENCE OF ERYTHEMA MARGINATUM

Carditis in Previous Attacks	Carditis at Time of Onset of Erythema Marginatum	Mitral Systolic Murmur	Mitral Diastolic Murmur	Aortic Systolic Murmur	Aortic Diastolic Murmur	Cardiac Failure	Additional Cardiac Signs Developing with Erythema Marginatum	β *Haemolytic strep.* in Throat when Erythema Marginatum Developed	Duration of Follow-up	Condition when Last Seen
−	+	+	+	+	+	−	−	+	3 yr.	Leading normal life. Normal heart
+	+	+	+	+	+	−	−	+	3 yr.	Leading normal life. Grade II apical systolic murmur and aortic diastolic murmur
+	+	+	+	−	+	−	−	−		
+	+	+	+	−	+	−	−	−		
+	+	+	−	−	−	−	−	+		Leading normal life. Normal heart
+	+	+	−	−	−	−	−	+	1 yr.	
+	+	+	+	+	+	+	−	+	1¼ yr.	Disease still active. Treatment C continues. Grade III apical systolic murmur
−	+	+	−	−	−	−	−	N.D.	1½ yr.	Leading normal life. Heart normal
−	+	+	−	+	+	−	−	N.D.	1¼ yr.	Leading normal life. Grade II apical systolic murmur and aortic diastolic murmur
−	+	+	+	−	−	−	−	−	8 mth.	Leading normal life. Grade II apical systolic murmur
+	−	+	−	−	−	−	−	N.D.		
?	+	+	+	−	−	−	−	+	4 mth.	Disease still active. Treatment D continues. Grade III apical systolic murmur and apical diastolic murmur
−	+	+	−	−	−	−	−	−	2½ yr.	Leading normal life. Normal heart
−	+	+	−	−	−	−	−	−	3½ yr.	Leading normal life. Normal heart
+	+	+	+	+	+	+	−	−	3½ yr.	Leading normal life. Cardiac enlargement. Mitral systolic and diastolic murmur, and aortic diastolic murmur
−	+	+	−	−	−	−	−	−	3 yr.	Leading normal life. Normal heart
+	−	−	−	−	−	−	−	−		
−	+	+	+	−	−	+	−	−	3 mth.	Disease still active. Mitral systolic and diastolic murmurs
−	+	+	−	−	−	−	Mitral diastolic murmur	−	3 yr.	Leading normal life. Cardiac enlargement. Apical systolic and diastolic murmurs
+	+	+	+	−	−	−	Friction rub. Aortic diastolic murmur	+		
−	−	−	−	−	−	−	−	N.D.	4 yr.	Erythema marginatum on two occasions following penicillin injection
−	−	−	−	−	−	−	−	+	2 yr.	Death
−	−	−	−	−	−	−	−	N.D.	7 mth.	Death
−	−	−	−	−	−	−	−	−	6 mth.	Leading normal life. Normal heart
−	?	+	−	−	−	−	−	−	3 yr.	Leading normal life. Grade II apical systolic murmur

N.D.—investigation not carried out.

Treatment C. Salicylates as in M.R.C. Trial

Aspirin. 1 grain per lb. body weight per day, or 150 gr. total dosage, whichever was less for first 48 hr. reduced to ¾ gr. per lb. per day or 150 gr., whichever was less for 5 days, reduced to ½ gr. per lb. per day for remainder of 6-week period (to be given every 4 hr. for 48 hr. and four times daily thereafter).

M.R.C. cases received procaine penicillin G. in aluminium monostearate on 1st, 4th, 7th and 10th days, 300,000 units to children of 60 lb. or less, and 600,000 units to those over 60 lb. Thereafter they received sulphadiazine, 0·5 g. daily, and 1 g. daily respectively, and this is being continued.

Treatment D. Salicylates in High Dosage

Sodium salicylate gr. 1½ (0·1 g.) per lb. of body weight daily initially, the dose being adjusted to maintain a serum salicylate level between 30 and 40 mg. per 100 ml., weekly estimations being made.

Oral penicillin was given prophylactically in doses of 200,000 units daily.

Erythema Marginatum Associated with Rheumatic Fever

Details of the 14 cases are summarized in Table 1. It will be seen that they did not all come under observation in their first attack. When further rheumatic manifestations appeared before the patient had returned to full activity, the term relapse is used.

Study of Table 1 shows that the rash may appear at any time during or after an attack of rheumatic fever. In 11 cases (Nos. 1, 2, 3, 4, 8, 9, 10, 11, 12, 13 and 14) it was present at the onset, and in three cases it made its first appearance later in the course of the disease, in Case 5 after four months, in Case 6 after two weeks and in Case 7 after five days.

The distribution of the rash was as described by the writers previously mentioned, in that there was a predilection for the trunk and proximal parts of the limbs, the face being spared. Irritation and desquamation did not occur. The lesions were evanescent, in many instances passing through the cycle of changes described above in the course of a few hours, fresh lesions then appearing to repeat the cycle. The total duration was extremely variable from two days only in Case 6 to intermittent appearances for over two years in Cases 9 and 11.

The presence of erythema marginatum could not be correlated with the height of the sedimentation rate, for, while it is true that the sedimentation rate was raised when the rash first appeared in all 14 cases, in five cases (Nos. 1, 5, 9, 10 and 11) fresh lesions continued to appear when a normal value had been reached and all other signs of rheumatic activity had subsided. A profuse crop of new lesions was associated with recurrence of activity in four cases (Nos. 2, 3, 12 and 14), but there were exceptions to this, as shown by Cases 7 and 9. Case 7 developed fever and erythema marginatum six months after his first attack of rheumatic fever when the sedimentation rate was 11 mm. in one hour. On admission to hospital, Case 9 had fever, polyarthritis, acute carditis, nodules and erythema marginatum. He was treated with cortisone for six weeks. There was a rapid response and within 14 days all symptoms had subsided, although fleeting erythema marginatum continued. After a fortnight without treatment he developed a temperature of 103° F. and complained of a sore throat. A profuse crop of fresh lesions appeared. No β *Haemolytic streptococci* were isolated from his throat and the sedimentation rate was 10 mm. in one hour. Neither arthritis nor carditis recurred and no fresh nodules were seen. The temperature settled within three days and the rash faded, but continued to appear at intervals for two and a half years. There has been no other evidence of rheumatic activity and his heart is now normal clinically.

Erythema marginatum was uninfluenced by salicylates, cortisone or A.C.T.H. in the doses given, although other manifestations of rheumatic activity such as fever, arthritis and elevation of the sedimentation rate usually subsided. Fresh lesions appeared throughout the period of treatment in every case except No. 12. This child's rash disappeared within seven days of starting treatment in his first attack and within two days in his second. In Cases 4, 13 and 14 there was an immediate rise of temperature and sedimentation rate with recurrence of arthritis when attempts were made to discontinue treatment, but erythema marginatum continued in spite of treatment.

Acute carditis was present in all 14 cases. It preceded the appearance of the rash in three cases (Nos. 5, 6 and 7). Nine children (Cases 1, 2, 4, 6, 7, 8, 11, 13 and 14) had severe cardiac involvement and it is almost certain that cardiac damage is permanent in three (Nos. 2, 11 and 14). At the time of follow-up examination six children have apparently normal hearts (Nos. 1, 3, 5, 9, 10 and 12), in three cases the disease is still active (Nos. 4, 8 and 13), and, although cardiac murmurs can still be heard in Cases 6 and 7, it is less than six months since signs of rheumatic activity disappeared.

The duration of erythema marginatum and the extent of cardiac damage bear no apparent relationship to each other, as the following cases show. Case 6 had a loud aortic diastolic murmur and a mitral systolic murmur when first seen. Erythema marginatum appeared 14 days later lasting for two days only. The cardiac signs have remained unchanged for 16 months, except for some diminution in intensity of the mitral murmur. Treatment was discontinued five months ago. Case 1 presented with chorea, nodules, erythema marginatum and acute carditis, mitral and aortic systolic and diastolic murmurs being heard. All evidence of rheumatic activity subsided within three months, but erythema marginatum continued for 18 months. He has now been followed up for three years and his heart has been normal clinically for the past year. Case 9 had an apical systolic murmur for 18 months which then disappeared. He still has fleeting erythema marginatum two and a half years after his attack of rheumatic fever.

Nodules were seen in eight of the 14 cases (Nos. 1, 2, 5, 6, 9, 11, 13 and 14) and fresh nodules appeared while the patient was having treatment in five (Nos. 2, 5, 6, 11 and 14). Erythema marginatum and nodules sometimes occurred together, but this was not always so as is shown by the following

examples. Case 2 was given salicylates in high dosage in her third attack of rheumatic fever and no fresh nodules or erythema marginatum appeared. In her first relapse she was admitted to the M.R.C. investigation. Numerous fresh nodules continued to appear for eight weeks in spite of treatment with A.C.T.H. and erythema marginatum was seen intermittently for seven months. Case 5 developed two nodules during the first fortnight of treatment with salicylates. Erythema marginatum occurred after four months of treatment by which time the nodules had disappeared. In Case 6 fresh nodules continued to appear for the first month after starting treatment and erythema marginatum was seen for two days only during this time.

Case 11 was treated with A.C.T.H. and fresh nodules continued to appear for five months and erythema marginatum for two and a half years. During the first three months erythema marginatum was profuse and on three occasions fresh lesions were associated with a crop of new nodules. Case 14 was treated with salicylates in his first attack. Fever and arthritis subsided rapidly, but he developed a mitral diastolic murmur and fresh nodules appeared for one month. Erythema marginatum continued for four months. Salicylates were given for one month in his second attack, but treatment was then changed to cortisone because fresh nodules and erythema marginatum continued to appear. The sedimentation rate had fallen from 53 mm. in one hour to 25 mm. in one hour. Cortisone was given for seven weeks and during this time no fresh nodules were seen, but the rash persisted and he developed a pericardial friction rub and an aortic diastolic murmur. As soon as cortisone was stopped a profuse crop of nodules appeared and the sedimentation rate rose from 3 mm. in one hour to 30 mm. in one hour. Salicylates were then given for 11 months. No fresh nodules appeared and the sedimentation rate fell to normal in two weeks. Erythema marginatum continued for nine months. Thus it will be seen that erythema marginatum and nodules both appear to be uninfluenced by treatment.

Bacteriological studies are complicated by the fact that patients often receive sulphonamides or penicillin at the onset of any febrile illness before admission to hospital, and once treatment was started all these children were given prophylactic sulphadiazine or penicillin, and those in the M.R.C. trial had four injections of a long-acting penicillin preparation in addition. It was found that throat swabs had been taken on 18 occasions when erythema marginatum was actually present and β *Haemolytic streptococci* were isolated in seven cases. The organisms were not grouped or typed.

Estimations of the serum antistreptolysin O titre (A.S.O.) were only done routinely on the six cases in the M.R.C. series. In all the children the figure was maximal at the onset of the attack of rheumatic fever and gradually fell to normal. It rose again in Case 12 when he was admitted in his second attack. Erythema marginatum was present at the beginning of the attack in all six when the A.S.O. titre was high, but subsequent appearance of the rash and its total duration could not be related to the level of the A.S.O. titre (Table 2).

Erythema Marginatum Unassociated with Acute Rheumatism

Five cases of erythema marginatum are described below, in four of which there was no question of the presence of acute rheumatism. In the fifth the diagnosis of rheumatic fever was possible, but considered to be unlikely.

Case 15. A 9-year-old boy with bronchiectasis developed erythema marginatum on the trunk and legs on two occasions following penicillin injections.

Case 16. A girl, 5 years of age, was admitted to hospital with extensive erythema marginatum and acute

TABLE 2

ANTI-STREPTOLYSIN O TITRE IN RELATION TO THE OCCURRENCE OF ERYTHEMA MARGINATUM

Case No.	Duration of Erythema Marginatum	Anti-streptolysin O Titre (units/ml.)															
		Time in Months															
		Onset	1	2	3	4	5	6	7	8	9	10	11	12	18	24	30	36
1	18 mth.	125	N.D.	50	N.D.	50	N.D.	50	50	50	50	50	50	<50	50	50	50	50
2	2 yr.	200	833	N.D.	50	50	50	50	50	50	50	<50	50	50	50	50		
9	2½ yr.	200	200	125	50	50	<50	<50	<50	<50	N.D.	<50	50	50	50	50		
10	9 wk.	333	200	125	50	50	50	50	50	50	50	50	50	50	50	50	50	50
11	2½ yr.	500	500	333	333	500	500	200	500	200	200	200	125	200	50	50	50	
12	A.1 7 days A.2 2 days	200	125	125	125	50	50	50	125	<50	<50	<50	<50	<50	<50	<50	2,500	

nephritis. The rash had been present intermittently for eight months before admission. She was discharged after three months, by which time the urine was normal, but the rash continued to appear. Four months later haematuria recurred and she was admitted to hospital for a further eight months. *β Haemolytic streptococci* were isolated from the throat. Red cells and casts disappeared from the urine, but albuminuria remained and she developed slight oedema of the face and limbs. Erythema marginatum persisted in spite of a course of systemic penicillin and antihistamine drugs in increasing dosage (mepyramine maleate up to 150 mg. six-hourly). Sodium salicylate was next tried, 15 grains being given six-hourly. The rash disappeared immediately and was not seen for three weeks. It appeared when the drug was discontinued and was uninfluenced by a second course of salicylates. The child was last seen five months after discharge from hospital and the rash was still occurring, albuminuria was present, and numerous granular and cellular casts were seen in the urinary deposit with occasional red cells. A trace of oedema of the legs and face persisted. She died four months later.

Case 17. A boy of 7 weeks, under observation because of failure to gain weight and occasional loose stools, had erythema marginatum of the legs and trunk for five days. He was afebrile and was not receiving drugs at the time.

Case 18. A boy of 7 years was referred to hospital with a diagnosis of ringworm. He was found to have typical erythema marginatum on the trunk and limbs. His mother said the rash had been present intermittently for two years. He had occasional migraine, but apart from this was very fit. There was no history of tonsillitis or acute rheumatism. Clinical examination was negative apart from the rash. No *β Haemolytic streptococci* were isolated from the throat, and the sedimentation rate was 6 mm. in one hour. He had been given aspirin and phenobarbitone for the headaches, but the rash was first seen at least a year before the drugs were given and it continues to appear although he had had no drugs for six months.

Case 19. A 3-year-old girl was admitted to hospital because she had developed profuse erythema marginatum after an attack of tonsillitis. On examination she was found to be febrile and a moderately loud (Grade II) systolic murmur was heard down the left border of the sternum. The sedimentation rate was 60 mm. in one hour, and *β Haemolytic streptococci* were not isolated from the throat. There were no other symptoms or signs of rheumatic fever. A diagnosis of probable rheumatic carditis was made and she received salicylates in high dosage for a month. Treatment was then discontinued because of doubt about the diagnosis. The temperature settled within a few days of starting salicylates and the erythema marginatum faded rapidly. The sedimentation rate fell to 26 mm. in one hour and remained between 20 and 40 mm. in one hour for two years, although she was in excellent health and leading a normal life. The heart murmur has not changed and it would almost certainly be regarded as functional were it not for the previous history, but in view of this, its significance remains in doubt.

The electrocardiogram and screening of the heart show no abnormality. Eighteen months after her first admission the child had another attack of tonsillitis from which she made a rapid recovery. Erythema marginatum was not seen.

Discussion

There can be little doubt that erythema marginatum and rheumatic fever are often related in some way, but this study throws no light on the nature of the relationship. The association of the rash with other manifestations of so-called rheumatic activity, as judged by elevation of the sedimentation rate, fever, arthritis, nodules and acute carditis, is quite inconstant and in the present state of our knowledge it would seem illogical to treat erythema marginatum with salicylates, cortisone or A.C.T.H. and unjustifiable to restrict a patient in any way on account of the rash, in the absence of other signs of rheumatic activity.

The observations confirm the findings of Lehndorff and Leiner (1922), Wallgren (1935), Perry (1937) and Keil (1938) with regard to the high incidence of carditis in cases of erythema marginatum. In the present series the rash was of no immediate prognostic significance, but a much longer follow-up will be required in order to determine whether erythema marginatum presages permanent cardiac damage, for if carditis has been present at any time the inexorable process of scarring with final permanent valvular damage may have been set in motion in spite of the fact that for some years the heart may appear normal on clinical examination.

The occurrence of undoubted erythema marginatum in conditions other than rheumatic fever indicates that it is a non-specific phenomenon, and in this respect it resembles erythema nodosum. The association with acute nephritis is of interest, as both these diseases are thought to follow infection with *Group A β Haemolytic streptococci*, but erythema marginatum and acute nephritis are rarely seen together.

Summary

Fourteen cases of erythema marginatum associated with rheumatic fever are presented. The rash varied in duration from two days to two and a half years and was uninfluenced by treatment with salicylates, cortisone or A.C.T.H. It is shown that erythema marginatum may persist when all other signs of rheumatic activity have subsided, and long after the sedimentation rate has returned to a normal value.

Carditis was present in all 14 cases. At the time of the last follow-up examination six children had apparently normal hearts, three had sustained permanent cardiac damage and in five the observation period was too short for final cardiac assessment.

Four cases of erythema marginatum unassociated with rheumatic fever are described, and a fifth in which the relationship is doubtful. Erythema marginatum is therefore a non-specific phenomenon.

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CHRONIC NEPHRITIS IN A NEWBORN INFANT

BY

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Renal disease other than that associated with congenital malformations is rare in the newborn infant. Formerly syphilis played an important role in the production of inflammatory renal disease in infants, but with modern methods of ante-natal care congenital syphilitic nephritis is almost unknown in this country.

Glomerular changes, consisting mainly of hyalinization and fibrosis of the glomerular tufts, were described by Herxheimer (1909) and by Schwarz (1928). These lesions were called 'congenital glomerulosclerosis' by Friedman, Grayzel and Lederer (1942) who reviewed the subject in some detail. More recently Swan (1944) and Tedeschi, Halpern and Ingalls (1953) have reported similar lesions in the kidneys of infants whose mothers had suffered from rubella during pregnancy. It is felt, however, that these changes are probably vascular rather than infective in origin and are not specific manifestations of infection by rubella virus.

True glomerulonephritis is regarded as being uncommon by Zuelzer, Charles, Kurnitz, Newton and Fallon (1951) and according to Potter (1952) is unknown in the newborn infant.

Recently, however, there have been three reports of glomerulonephritis occurring in newborn infants (Thompson, 1951; Collins, 1954; Kunstadter and Rosenblum, 1954). These authors regarded the condition as an extreme rarity and were unable to find reports of similar cases in the literature. Lapage (1932) had described a case of acute haemorrhagic nephritis in the newborn, but glomerular changes were absent.

In this paper we describe a case of nephritis in a newborn infant. The renal changes were most severe and affected the glomeruli, tubules and interstitium.

Case Report

The mother was a healthy woman of 29 years of age, and this was her third pregnancy. Her first pregnancy in 1948 resulted in the birth of a female child who subsequently showed pyloric stenosis. She had a healthy female child as a result of her second pregnancy in 1951.

During the pregnancy she seemed quite well until the beginning of the third month when she had a mild throat infection. A more severe throat infection occurred during the fifth month. Similar attacks had occurred during the previous two years. She was first seen during the seventh week of her pregnancy. Blood pressure was 115/70 mm. Hg and her urine contained no abnormal constituents. Wassermann and Kahn reactions were negative. Her haemoglobin was 13·5 g. % and she was Group O Rh positive. No abnormality was seen in a radiograph of the chest. The patient thereafter attended her local county council ante-natal clinic until the 36th week when she was again seen at hospital. No abnormality was found at this examination.

Labour began spontaneously on August 9, 1954, 19 days before the estimated date of delivery. On admission to hospital a breech presentation of the foetus was diagnosed. The membranes were still intact but the foetal heart was irregular. Breech delivery was effected two hours later. The placenta weighed 794 g. The puerperium was uneventful. On November 15, 1954, her throat was clear. A swab yielded no pathogens. The anti-streptolysin titre of the blood was 200 units/ml. Blood urea was 22 mg./100 ml. and uric acid 1·7 mg./100 ml. The patient was a male infant of 6 lb. 13 oz. (3,091 g.) birth weight. He was apnoeic at birth, had a feeble cry and took infrequent gasps. He improved after assisted breathing in a servo-respirator but indrawing of the chest persisted. Crepitations were present in both lung fields. On radiological examination, bilateral pneumothorax was found. The infant died aged 10 hours.

Necropsy. The body was that of a well developed male infant weighing 3,175 g. No congenital abnormality was found on external examination. The tentorium was torn on both sides and there was severe bilateral subdural haemorrhage. The brain was normal.

The larynx, trachea and bronchi were healthy. There was a pneumothorax on the left side. The lungs were congested and poorly expanded. The right lung was atelectatic and sank in water. The left lung floated as a result of gross emphysema. Large emphysematous bullae were present in the interlobular fissures.

The heart and great vessels were normal.

A few petechial haemorrhages were present in the small intestine. The liver and pancreas were healthy.

The kidneys were quite large (each weighed 26 g.). Their appearance was similar. They showed foetal lobulation and the capsule stripped easily. Their surface was generally smooth, but a few minute cysts, 0·5-1 mm. diameter, were present. The cysts had smooth walls and contained a little fluid. Numerous petechiae were present over the surface of the kidneys. On slicing the cortex and medulla could be easily differentiated. The cortex was congested and numerous silvery streaks were seen running at right angles to the surface. Occasional small cysts were seen. The pyramids showed a few small haemorrhages. The calyces and pelvis were healthy. The renal vessels appeared normal and the ureters and bladder were healthy.

The spleen appeared normal. The suprarenal glands, thymus, thyroid and pituitary glands were healthy.

Histology. The left lung showed numerous subpleural emphysematous bullae. Patchy intra-alveolar haemorrhage was seen in both lungs. The right lung was unexpanded. There was no pneumonia.

The liver and spleen showed no abnormality.

The capsule of the kidneys showed little change. The glomeruli were reduced to about one-third of their usual number. Of the remainder, few were completely normal. Many were atrophic and showed periglomerular concentric fibrosis (Fig. 1). A few showed proliferation of the cells of Bowman's capsule with striking crescent formation and in some cases the capsular space had been obliterated by this process (Fig. 2). Pseudocrescent formation was also observed in a number of instances (Fig. 3). Here the glomeruli showed partial hyalinization and a neighbouring convoluted tubule was becoming adherent to the glomerular capsule. The latter showed epithelial proliferation and eventually the complex would have become hyalinized and surrounded by fibrous tissue. The end-result would therefore be almost indistinguishable from the crescent described above (Fig. 2). In other glomeruli capsular proliferation was less pronounced, but some adhesions were present between the glomerular tufts and the capsule. In a few instances the capsular space contained acidophile material with an occasional polymorphonuclear leucocyte. Glomeruli undergoing atrophy were present throughout the cortex, but those exhibiting proliferative change were more frequently found near the cortico-medullary junction.

The tubular changes were even more striking. The small superficial cortical cysts seen on macroscopic examination proved to be grossly dilated tubules containing acidophile fluid. About half the cortical tubules were dilated and contained colloid casts (Fig. 1). This gave the kidney a thyroid-like appearance. The dilated tubules were lined by flattened atrophic epithelium. The convoluted tubules were more affected than the collecting tubules but the latter also showed cyst formation. A few convoluted tubules showed true hypertrophy and their epithelium was thrown into papilliform

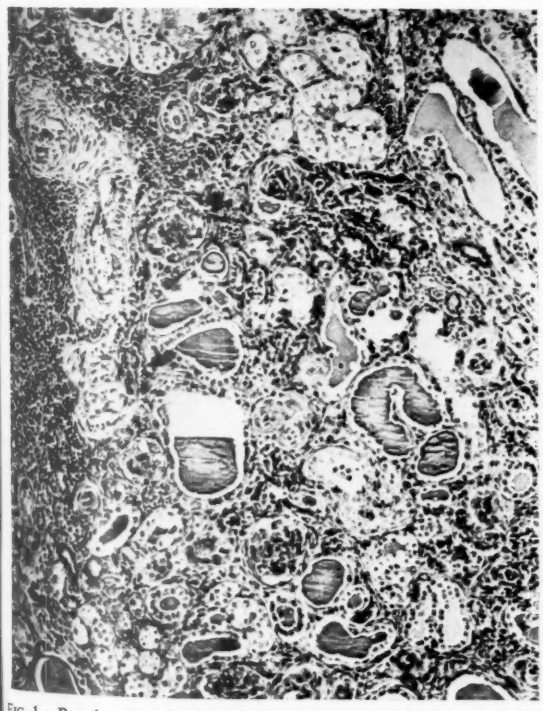

FIG. 1.—Renal cortex showing glomerular atrophy, tubular dilatation and colloid casts in the convoluted tubules. Large haemopoietic foci are present on the left. Haematoxylin and eosin ×75.

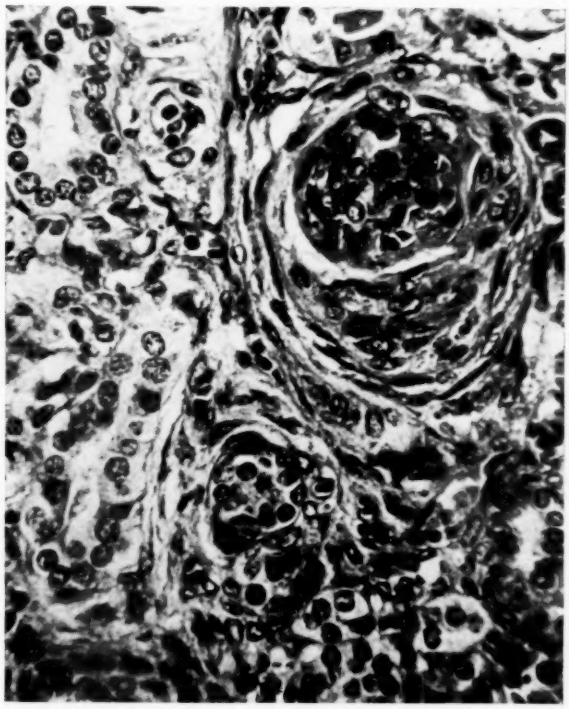

FIG. 2.—Glomerulus showing partial hyalinization of the tuft and epithelial cell proliferation of the capsule with crescent formation. Haematoxylin and eosin ×375.

folds. In addition to the acidophile colloid material a number of tubules contained polymorphonuclear leucocytes and cellular debris. Only very few tubules, however, contained purulent material and the majority contained no cells at all. A few tubules showed erosion of their walls by an inflammatory process and numerous leucocytes were present.

In addition to cystic dilatation a number of convoluted tubules showed pronounced hyaline droplet degeneration of their lining cells (Fig. 4). Their cells were pale and swollen and in places the epithelium was replaced by bright acidophile droplets. A number of convoluted tubules showed severe hyaline change and their epithelium was converted into a hyaline band (Fig. 5). In some cases two or more such hyalinized tubules had fused. No cytoplasmic inclusion bodies were seen and no organisms were found in sections stained by Gram's method.

The interstitial tissue also showed marked alteration. There were numerous large foci of extramedullary haemopoiesis throughout the cortex (Fig. 1). These were mainly normoblastic in character but there was also a considerable amount of leucopoiesis. In addition to these foci small aggregations of polymorphonuclear leucocytes and some lymphocytes were present in the peritubular connective tissue throughout the cortex. This inflammatory cell infiltration was chiefly evident in the cortex and was minimal in the medulla.

Small haemorrhages were present throughout the cortex. They were situated chiefly in the boundary zone between the cortex and the medulla. A few haemorrhages were also seen in the peripelvic connective tissue.

The interstitial connective tissue was increased in amount. This fibrosis was mainly cortical. Perivascular fibrosis was most pronounced and long strands of fibrous tissue were present in the medullary rays. These were responsible for the silvery streaking noted on macroscopic examination. The convoluted tubules were also surrounded by thickened fibrous tissue bands. The collecting tubule interstitium showed little change. There was some increase in the peripelvic connective tissue which showed slight polymorphonuclear leucocytic infiltration. The epithelium of the renal pelvis was healthy (Fig. 6). There had been some upset in renal development as a result of the inflammatory process. The outer cortex, which is the neogenic region of the organ, showed the most pronounced effect. Small groups of tubules were surrounded by concentric rings of fibrous tissue and glomeruli were absent.

The renal vessels were most noticeable for the amount of perivascular fibrosis. A number of arterioles showed hyperplastic sclerosis. Vessels in other organs were quite normal.

Discussion

In spite of the signs of glomerulitis and crescent formation in this case we believe that the fundamental lesion is a chronic, but still active, pyelonephritis. The gross dilatation of the cortical tubules which contained colloid casts, the presence of pus in a number of tubules, the increase in the interstitial connective tissue which showed infiltration with polymorphonuclear leucocytes and the glomerular atrophy with concentric pericapsular fibrosis all point to this diagnosis. We feel that only a few glomeruli showed truly proliferative lesions and these were insufficient to account for the gross alteration of the cortical architecture. The glomerular changes were probably the result of an 'alterative glomerulitis'. This change has been described in pyelonephritis by Kimmelstiel and Wilson (1936). These authors have shown that in some cases of pyelonephritis there is hyalinization of some loops of the glomerular tuft with the formation of capsular adhesions. Occasionally this is followed by capsular proliferation. They also describe a process of 'invasive glomerulitis' which probably explains the pseudo-crescent formation we observed in the kidneys of our case. In this instance there is a direct extension of the inflammatory process from the interstitial tissue, periglomerular lymphatics or tubules through the capsule into the glomerular space and tuft. This process was quite clearly demonstrated in our case (Fig. 3). A tubule containing polymorphonuclear leucocytes is seen adhering to the capsule of a glomerulus. The tubular epithelium nearest to the capsule is undergoing necrosis and will eventually become adherent. A neighbouring glomerulus in the same field shows a further stage in this process. The tubular lumen is now only a narrow cleft and the glomerulus and tubules have formed a complex mass. The capsular epithelium undergoes proliferation and eventually the whole mass is hyalinized and surrounded by concentric rings of fibrous tissue. The presence of pus in the tubules and of polymorphonuclear leucocytes in the interstitial tissue suggest that the process was still active, but these findings were not striking features of the case.

Recently Collins (1954) described a case of chronic glomerulonephritis in a newborn child who died 90 hours after birth. The illustrations indicate that the renal changes in his patient were almost exactly similar to those reported above. Collins favours a diagnosis of 'chronic and subacute glomerulonephritis' instead of pyelonephritis. He excludes the latter largely on account of the severe glomerular changes in the comparative lack of inflammatory cell infiltration.

Thompson (1951) reported the occurrence of nephritis in a child who lived for 29 days after birth. The infant during this period suffered from oedema and albuminuria. Red cells, pus cells, hyaline and granular casts were present in the urine. Histological examination of the kidneys showed hyaliniza-

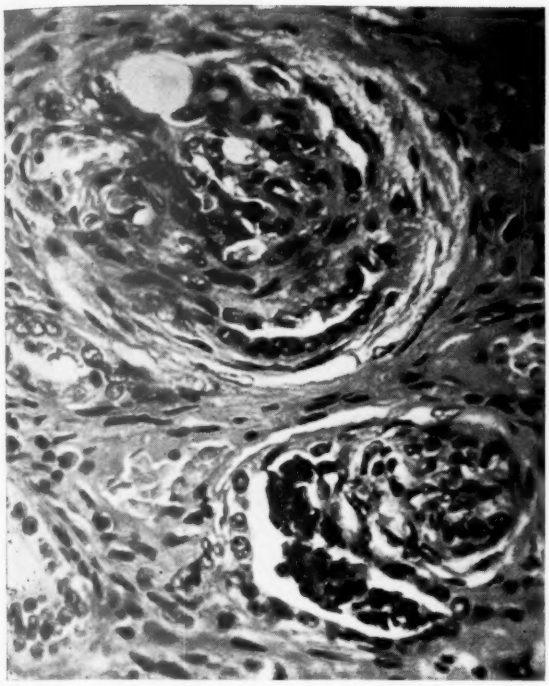

FIG. 3.—Two glomeruli with adherent tubules. On the top left the convoluted tubule is a narrow slit attached to the glomerular capsule and surrounded by fibrous tissue. On the right the tubule contains pus cells and debris. The inner wall of the tubule is becoming attached to the glomerulus. Haematoxylin and eosin ×375.

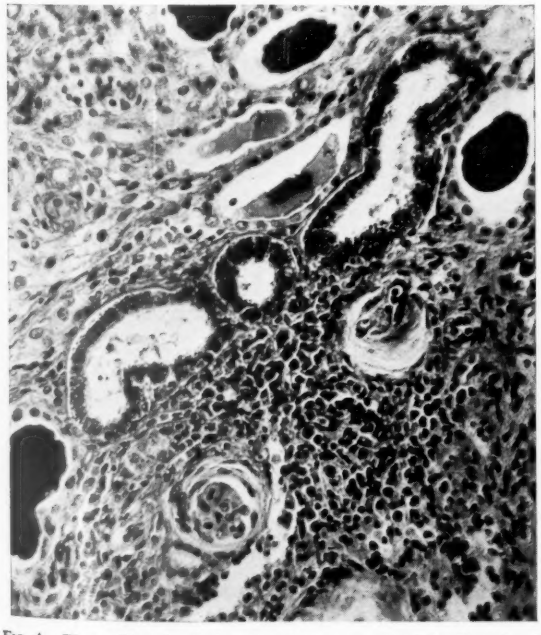

FIG. 4.—Three dilated tubules showing pronounced hyaline droplet degeneration. Picro-Mallory ×175.

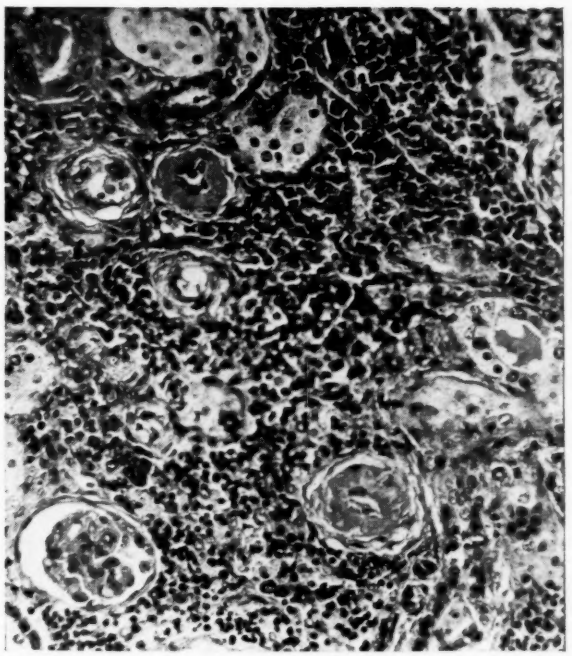

FIG. 5.—Renal cortex showing two completely hyalinized tubules with peritubular fibrosis. There is marked haemopoietic activity in the interstitium. Haematoxylin and eosin ×175.

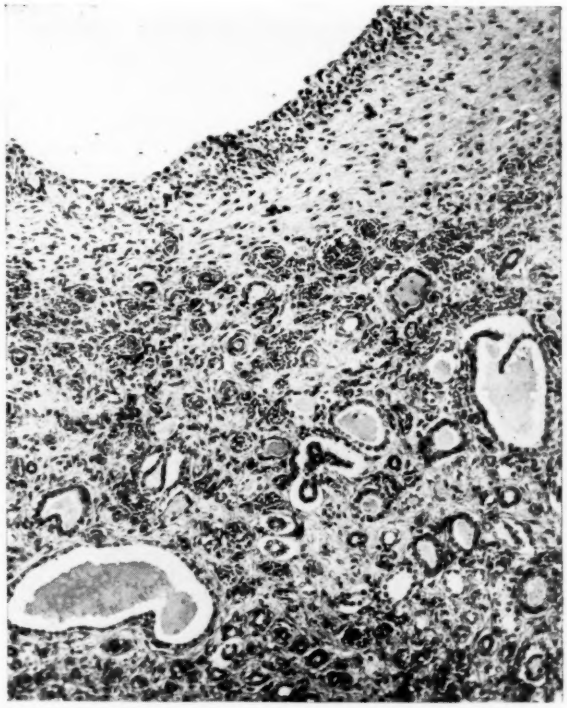

FIG. 6.—Medulla and pelvis. The stratified epithelium of the pelvis is intact. The subepithelial connective tissue shows slight infiltration with polymorphs. The medulla is congested and dilated tubules contain colloid casts. Haematoxylin and eosin ×75.

tion of some glomeruli while others showed capsular adhesions, crescent formation and increased cellularity of the tufts. The proximal convoluted tubules were lined by a partially vacuolated epithelium and the collecting tubules contained casts and leucocytes. There was marked periarterial fibrosis and the arterioles showed hyperplastic sclerosis. The periarterial fibrosis was explained on the basis of hypertensive change. The author believes that this was a case of glomerulonephritis of some standing. The considerable pyuria and the cellular infiltration of the renal stroma suggest that this view may be incorrect and that this was possibly another example of pyelonephritis.

More recently Kunstadter and Rosenblum (1954) have described a case of neonatal glomerulonephritis and the nephrotic syndrome. The infant was born prematurely and died 72 days later. During this time the infant had shown pitting oedema over the face and trunk. The infant was very anaemic and required several blood transfusions. The urine contained albumin, red cells and casts. At necropsy the kidneys showed reddening of the cortico-medullary junction and yellow streaking perpendicular to the cortical surface. On histological examination the glomeruli were small, hyperaemic and more cellular than usual. A few glomeruli showed proliferation of the cells of Bowman's capsule with some adhesions. The tubular epithelium was swollen, granular and vacuolated. The authors believe that this was an example of subacute glomerulonephritis with nephrosis.

Not one of these recent accounts shows that the diagnosis of glomerulonephritis has been established beyond any reasonable doubt, and Potter (1952) is probably still correct in her opinion that it does not occur in the newborn.

The pathogenesis of nephritis in the newborn is obscure. Collins (1954) and Thompson (1951) have suggested an allergic or hypersensitivity basis for the occurrence of glomerulonephritis in their patients.

It is interesting to note that the mother of the child reported by Thompson had suffered from a sore throat during the sixth month of her pregnancy. The mother of the infant in the present case had a throat infection twice during her pregnancy, at the third month and again during the fifth month. Whether a hypersensitivity phenomenon following on these throat infections during early pregnancy could explain the occurrence of a pyelonephritis in the present case is rather doubtful. There are certain features which favour such a supposition. The entire histological picture is rather unusual. While we are satisfield that this is not a true glomerulonephritis, the pronounced glomerulitis and tubular hyalinization are peculiar features. Furthermore, the intense perivascular fibrosis and pronounced periarterial cellular infiltration bear a faint resemblance to the appearance found in the healing stages of polyarteritis nodosa. The latter has been ascribed to a hypersensitivity reaction. The lack of severe inflammatory change in the renal calyces and pelvis also suggests that we are not dealing with a typical bacterial infection of the kidney.

If this pyelonephritis is to be regarded as the result of a bacterial infection we have to decide the source of infection and there seem to be only two possibilities: first, a maternal bacteraemia with transmission of the organisms to the foetal blood stream via the placenta, or secondly an infection of the liquor amnii which is then swallowed by the foetus and absorbed from the gut. The first explanation is improbable since organisms are unlikely to pass the placental barrier without causing a placental lesion and there was no evidence of this in the present case. The second supposition is more plausible, but there is no evidence that it did occur. The liquor amnii was not malodorous and no inflammatory lesions were found in the infant's lungs. There is thus no clear evidence to support the infective origin of the renal lesions and no organisms were found in the sections examined.

The changes in the renal cortex which were found in the present case are of special interest since they would seem to form the basis of the so-called 'chronic interstitial nephritis' in older children which was described by Mitchell (1930). A case of a slowly progressive nephritis associated with marked skeletal changes in a child of 5 years has already been recorded by one of us (Claireaux, 1953). The kidneys in this patient showed marked glomerular hyalinization with pericapsular fibrosis and severe interstitial fibrosis. A number of tubules contained pus. There was no congenital abnormality of the urinary tract. It is almost certain that this was an example of a chronic but still active pyelonephritis. Weiss and Parker (1939) are firmly convinced that all these cases of so-called interstitial nephritis associated with renal dwarfism are, in reality, examples of chronic pyelonephritis. Thus older infants and children who show an osteodystrophy associated with advanced renal disease have almost certainly suffered from pyelonephritis for some considerable time. Craig (1935) has shown that acute pyelitis and pyelonephritis are not uncommon in the neonatal period. The majority of patients recover but in a few instances the renal disease may become chronic with the development of hypertension and bone lesions in later life. The case

we have described above would seem to indicate that the fundamental renal lesion can occur even *in utero*.

Summary

A case is reported of chronic pyelonephritis in a newborn infant. In addition to advanced tubular changes the kidneys showed unusual proliferative lesions in the glomeruli which may sometimes be mistaken for glomerulonephritis.

The pathogenesis of this condition is obscure, but is possibly the result of a hypersensitivity reaction to an infection in the mother during early pregnancy.

It is suggested that this unusual form of pyelonephritis may form the basis of the so-called chronic interstitial nephritis found in older children with renal osteodystrophy.

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HYPOGLYCAEMIC COMA

BY

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Symptoms of hypoglycaemia have only been recognized since the introduction of insulin. Since that time they have been noted in connexion with syndromes other than the over-production and overdosage of insulin, and the symptom-complex has become a well recognized entity. Most of these non-pancreatic causes of hypoglycaemia do not lead to coma. A low blood sugar level may be found in Addison's disease, Simmonds' disease and myxoedema and in conditions of chronic hepatic insufficiency, in malnutrition, and following prolonged, severe exercise. In von Gierke's disease there is a lowered blood sugar level, although the patient rarely complains of symptoms relative to hypoglycaemia.

The pancreatic causes of hypoglycaemia are (*a*) tumours of the islet tissue, and (*b*) the condition of hyperinsulinism; the hypoglycaemia in both these conditions may be sufficiently severe to precipitate the patient into coma. During the stabilization and maintenance of insulin therapy such episodes often occur and occasionally may lead to crippling mental or physical sequelae.

Finally, overdosage of insulin will cause hypoglycaemia as exemplified in our case which is reported here.

Case Report

L.W., a white child aged 2 years and 1 month, was admitted in coma to the Transvaal Memorial Hospital for Children on April 30, 1953. The child was a diabetic and was well controlled on 10 to 15 units of N.P.H. insulin each morning. Since her discharge from hospital six weeks before, when her insulin dosage had been stabilized, she had developed and recovered from a mild diarrhoea and upper respiratory tract infection.

The mother stated that she had felt that the child would be cured of her diabetes if she remained sugar-free for a period of time. She had consequently increased the insulin dosage above the prescribed level and had at the same time restricted the child's diet. The child had been irritable for some time and had tended to become inattentive and 'dreamy'; the mother had also noted that this was worse before meals. This querulousness and inability to concentrate had become worse in the few days before admission, although it was not attended by signs other than occasional twitching of the left hand for three days before admission. This state of affairs culminated in the parents finding the child unconscious early one morning. Before admission to this hospital the child had been unconscious for 17 hours in another hospital where initially insulin had been given and intravenous glucose administered later, but no control blood sugar estimations done. The child had been energetically treated for 'shock', this including the application of hot-water bottles to secure warmth.

On examination the child was deeply comatose with involuntary movements of the left face, arm and leg. The face and hand twitched continuously, whilst the leg was less affected. The urine was sugar-free.

All other systems were clear.

Examination of the cerebrospinal fluid excluded other central nervous system conditions, such as encephalitis. The physical findings, combined with such a definite history of insulin overdosage, were so typical that a diagnosis of hypoglycaemic coma was made, despite the finding of a normal blood sugar level after admission, which it was felt, was due to the intravenous administration of glucose before admission.

A full blood examination on the day of admission gave the following results: Haemoglobin 15 g., erythrocytes 5,000,000, leucocytes 14,500, blood sugar level 202 mg. %, serum potassium level 19·2 mg. %, and serum sodium level 283 mg. %. Four hours after admission the blood sugar level was 324 mg. %, and 12 hours after admission it had fallen to 122 mg. %. On May 1 the cerebrospinal fluid was examined, when no cells were seen, protein was 10 mg. %, chloride 700 mg. % (as NaCl) and sugar 66 mg. %.

On admission an intravenous infusion of isotonic saline was begun and 40 ml. of 50% solution of glucose administered intravenously. On receipt of the laboratory reports insulin was also given. Insulin dosage was guided by the amount of sugar in the urine, tested four-hourly. During the first 60 hours a total of 500 ml. of normal saline and 1,000 ml. of 5% dextrose in normal saline and 2,000 ml. of 5% dextrose in water was given (Fig. 1). Vitamin B1, 1,000 mg., and vitamin C, 100 mg., were added daily to the infusion.

On the third day cortisone therapy was instituted in

TABLE 1
DETAILS OF TREATMENT

Day	Insulin (units)	Cortisone (mg.)	Vitamins (units)	Penicillin (units)	Sedation	Fluids (ml.)
1	10	Nil	Nil	400,000	Nil	500 normal saline
2	10	Nil	1,000 Vit. B_1 100 Vit. C	do.	Nil	1,000 5% dextrose/normal saline
3	5	50	do.	do.	Phenobarbitone gr. 11	2,500 5% dextrose in water
4	26	50	do.	do.	do.	2,000 5% dextrose/water
5	16	40	do.	do.	do.	do.
6	16	30	do.	do.	do.	do.
7	22	20	do.	do.	Nil	Oral fluids

view of its glycogenic properties, and 50 mg. was given daily for two days and then decreased by 10 mg. daily (Table 1).

From the sixth day the level of consciousness improved and the jerking grew less. The child at this stage responded to painful stimuli. By the eighth day she was fully conscious, but extremely irritable and still manifested occasional twitching of the left arm, hand and leg. It was noted at this time that the patient could not use the left arm and that the left leg was weak.

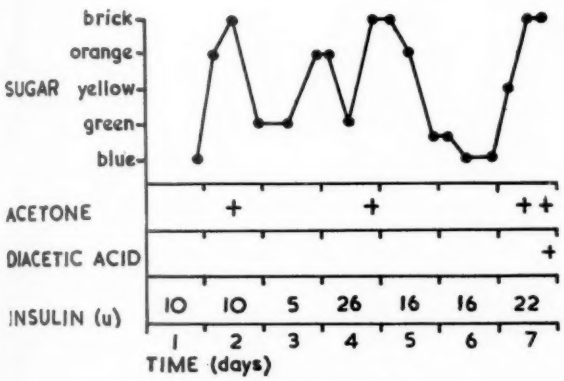

FIG. 1.—Chart of urine analysis.

The child remained in hospital for a further three months during which time a gradual improvement in the left facial palsy and the left leg were noted. The left arm, however, did not improve as much and on her discharge from hospital she still had a considerable paralysis of this limb. During this time the left arm and leg twitched almost daily, but no loss of consciousness was associated.

An air-encephalogram (Fig. 2) was performed on July 27 and Dr. H. Jackson reported that there was dilatation of the right lateral ventricle with displacement to the right. This suggested right cerebral atrophy.

The child has now been followed for 18 months since admission, and this period has seen worsening of the fits. At first they took the form of jerks of the arm, but gradually she started to manifest absences and about 12 months after admission to hospital, akinetic seizures began to make their appearance. Major epilepsy is also present, but these attacks are not as frequent. Attacks of one or other type of epilepsy occur up to 20 times a day, the child falls frequently, and is never without evidences of trauma.

She appears lethargic and the mother has noted that she cerebrates slowly and has learned very few new words since her discharge from hospital. During the early phase of recovery she spoke very little. The mother feels that there is definite mental retardation. The left hemiplegia remains stationary and there is also a degree of dysarthria which shows itself in a thick, slurred speech.

The diabetes remains as before, but she is reasonably well controlled on 10 units crystalline insulin and 10 units P.Z. insulin each morning combined with a free diet.

A Merrill-Palmer intelligence test was given and the following results were obtained:

Chronological age	3 years 8 months
Mental age	2 years 3 months
I.Q.	61

During the test the child was extremely distractable; she was unable to give her full attention to the test. When presented with a test item, she was vague as to

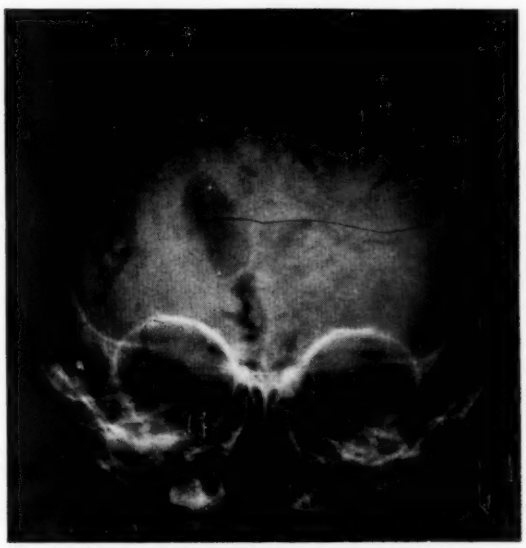

FIG. 2.—Postero-anterior air encephalogram.

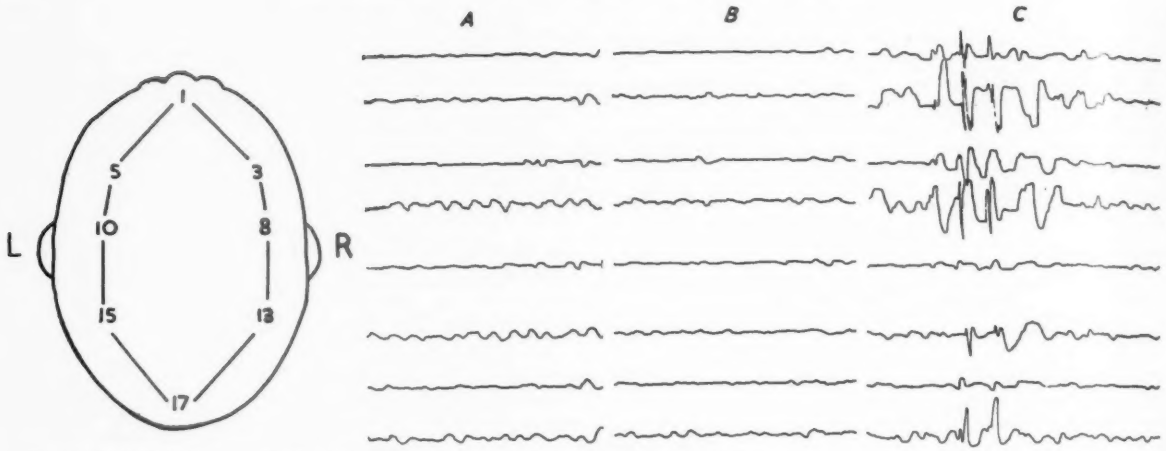

FIG. 3.—E.E.G. tracing on October 13, 1954. A shows asymmetry, B a flat record, and C spikes during an episode. Positions 1 and 2.

what was required of her. She had a low frustration tolerance and gave up easily. She worked for a short time with a test item, and, being faced with apparent failure, she appeared to become irritated by her inability to succeed. This was followed by a short temper tantrum, during which she pushed the items off the table on to the floor.

She reacted indifferently to praise. When she wanted to stop working on a test item, no amount of praise or encouragement was effective in keeping her at her task.

She was able to name objects, but was unable to explain their use. Vocabulary was extremely limited, spontaneous speech consisting of one or two-word sentences, often unintelligible. When asked to repeat sentences, responses consisted of 'unintelligible baby talk'.

An E.E.G. (Fig. 3) was done on October 13 and Dr. M. K. Wright reported that there was an area of diminished amplitude over the right central and parietal areas, and also a definite spike focus on the convexity of the left frontal lobe. Such spike foci commonly shift in young children. The E.E.G. suggested that there had been rather diffuse cortical damage rather than a localized lesion.

Discussion

The morbid anatomical findings following hypoglycaemic coma may be widespread, and Lawrence, Meyer and Nevin (1942) have indicated several different pathological changes. There may be complete necrosis of nerve cells over areas of the cerebral cortex and these areas may be remarkably circumscribed. In addition to the necrotic lesions there are areas of lesser damage in which cells are not completely destroyed. There may also be gross vascular lesions in the cortex and basal ganglia. Lawrence *et al.* (1942) compare these changes to the damage in the central nervous system following severe anoxaemia due to causes as dissimilar as poisoning with cyanide, carbon monoxide and ether, status epilepticus and cardiac arrest during anaesthesia. The two cases of Roche (1942), both of which came to necropsy, had cerebral changes; the first showed perivascular softening in the thalamus, caudate and lenticular nuclei, and the second a generalized softening, especially in the cerebellum. Hicks (1950), in animal experiments, showed that the administration of insulin to rats in dosages sufficient to cause convulsions often led to destruction of nerve cells of the cerebral cortex and corpus striatum; the basal nuclei were occasionally affected. Grayzel (1934) in experiments performed on rabbits found that in hypoglycaemic animals in which convulsions occurred brain damage was marked, whereas in rabbits in which the dose of insulin was insufficient to cause convulsions minimal or no microscopic evidence of necrobiosis was found. The brain damage in these patients is due to the fact that nerve cells require glucose for their oxidative processes. The cells, however, carry a very small reserve of glucose and have to replenish these stocks from the blood glucose. Thus, in cases in which the blood sugar level falls too low the cell metabolism becomes grossly impaired, resulting in severe damage to or actual death of the cell. The failure of this essential oxidative process leads to the final picture which is similar to that found in anoxic damage to the brain.

Tyler (1941), working with cats, found that the higher the dose of insulin the greater the brain damage, and that the giving of phenobarbitone tended to ameliorate the symptoms. In addition, cats at a low temperature tended to receive less damage to the central nervous system. Cerebral metabolism is depressed by both hypothermia and by the administration of barbiturates, leading to a lessened oxygen uptake, and therefore a lessened

need of oxygen, which is obviously desirable in hypoglycaemia. The higher the dosage of insulin in these animals, the more protracted was the fall in blood sugar and the greater was the amount of glucose required to terminate the hypoglycaemia.

The symptoms of hypoglycaemia vary somewhat with the type of insulin used, but are basically the same for both short- and long-acting insulins. They commonly appear several hours after the administration of crystalline insulin, but may occur much sooner if the patient has taken no food or has had to take violent exercise in the interim. The long-acting insulins—globin insulin, N.P.H., P.Z. insulin and the 'lente 'insulins—have their maximum effects later, the symptoms are less spectacular and the patient's attention is not drawn to them so readily. He slips quietly and unobtrusively into a stuporous state. The response to the administration of glucose by mouth or by intravenous injection is usually quick. It should, however, be remembered that long-acting insulins continue to act after the blood-sugar has been restored to normal and that frequent doses of sugar must be administered.

The difficulty encountered in our case in terminating the coma, despite adequate treatment, has been recorded elsewhere (Klein and Ligterink, 1940). The longer the patient has been in coma the more difficult it is to terminate the condition (Joslin, Root, White and Marble, 1952). Lawrence *et al.* (1942) state that coma of up to three hours is usually associated with complete recovery, while coma of longer duration is dangerous. Layne and Baker (1939) make the observation that the return of the blood sugar to normal has little effect on the duration of coma. It is important to maintain a normal or rather high blood sugar level during the state of recovery. In our case the observations of Klein and Ligterink (1940), Layne and Baker (1939) and Joslin *et al.* (1952) are well brought out; this child had a raised blood sugar level on admission to this hospital after having had intravenous glucose in the outside hospital. This is also in accord with the experimental evidence of Tyler (1941), who found that many of the cats used in his research work remained comatose for several days despite a normal blood sugar level.

Hypoglycaemic coma with cerebral damage may lead to progressive mental deterioration and to organic brain damage which may manifest itself clinically as paralysis or epilepsy. Anderson (1940) reports two cases. In one the child's mental age after the onset of coma at 13 years was 5½ years, and in the other child the mental age at 7 did not exceed 4 years. In the first case the child's memory improved, but the second patient had to be placed in an institution. Allan and Crommelin (1942) report a child, aged 6 years, in whom some degree of mental dullness remained months later. In several cases of hypoglycaemic coma reported by Graham (1950) (all adults) the patients had mental changes of a degenerative nature.

Klein and Ligterink (1940) report two cases of hypoglycaemic coma followed by mental retardation. Gardner and Reyersbach (1951) record a case of progressive mental deterioration following brain damage, despite the avoidance of further hypoglycaemia. Murphy and Purtell (1943) in reviewing 26 cases from the literature, eight of which died, record six instances of mental defect, and a further six cases described as personality changes, mental changes, organic psychosis, mental confusion and 'mental invalid'. Two children, one aged 8 and one aged 15, in a series of seven cases reported by Layne and Baker (1939) both showed mental retardation. The older child manifested epilepsy and was ataxic. Several of McQuarrie's (1954) cases of convulsions and coma due to spontaneous hypoglycaemia are mentally retarded and show damage in the central nervous system.

The organic changes may result in paralysis or epileptic seizures, and in all the cases quoted above either organic changes or convulsions occurred. Several cases in the literature, quoted by Murphy and Purtell (1943), were aphasic either permanently or temporarily, but it was not stated whether this was due to mental change or brain damage. In their own case they report mental change and temporary paralysis and the aphasia was obviously due to the mental condition.

The case of Gardner and Reyersbach showed a progressive deterioration in the E.E.G. and that child had convulsions which were extremely difficult to control; in addition, air studies showed definite enlargement of the lateral and third ventricles. In electroencephalographs done on 35 diabetic cases with repeated insulin reactions by Greenblatt, Murray and Root (1946) there were 18 definitely abnormal, nine borderline and eight normal. In our case the E.E.G. was abnormal and an air study showed enlargement of the right lateral ventricle.

The present state of our patient fits in well with the description of mental retardation, frequent epileptiform seizures and hemiplegia referred to by various authors. The convulsions as exhibited in our case are extremely difficult to control and consist of grand mal seizures, petit mal absences and akinetic attacks. The child's response to all forms of medication has been poor. The trigger mechanism, according to the parents, may be either hypoglycaemia or acidosis. Engel, Halberg, Ziegler and

McQuarrie (1952), in very complete studies on two children with epilepsy following hypoglycaemic coma, found that no correlation could be determined between seizures and the blood sugar level. These authors showed that there is, however, less association of the spike-and-wave activity at $2\frac{1}{2}$ per sec. with hypoglycaemia than with hyperglycaemia.

McQuarrie (1954) treated 25 cases of spontaneous hypoglycaemia with cortisone or corticotrophin with very good results. This was also done in our case, and in our opinion should be part of the treatment of similar patients in future, particularly in those cases caused by long-acting insulins.

In the light of the experimental work of Tyler (1941) these comatose patients should perhaps be sedated and subjected to hypothermia. The practical application and degree of hypothermia remain to be determined. It would appear physiological not to warm the patient, and it is possible that the warmth applied to our patient before her transfer to this hospital may have contributed towards the noxious effects of the hypoglycaemic state. In view of recent work on hypothermia during cardiac surgery, this treatment may possibly be tried in future cases. It must be noted that the cats in Tyler's experiments were not 'cooled', they were merely not 'warmed'. There was a drop in temperature of about 6° C. in these animals by the time coma had set in, and this appeared sufficient to ward off a large degree of brain damage.

Summary

A case of hypoglaemic coma is recorded and the pathology discussed. The clinical observation is made that coma may persist for many days despite the restoration and maintenance of a normal blood sugar level. The final state of severe brain damage manifesting itself as convulsive episodes, mental defect and hemiplegia is described.

The literature is briefly discussed.

The suggestion is made that cortisone, sedation and hypothermia may be useful adjuncts in the therapy of this condition.

We would like to thank Dr. K. Mills, Medical Superintendent, the Johannesburg Group of Hospitals, and Dr. J. J. Theron, Assistant Visiting Paediatrician at the Transvaal Memorial Hospital for Children, for permission to record this case, Mr. S. Shevitz, of the Department of Medicine of the University of the Witwatersrand, for the radiographs, Dr. M. Wright for the E.E.G. tracings and reports, and Dr. S. Heymann, Head of the Department of Paediatrics, University of the Witwatersrand, for the interest he has taken in this paper.

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HYPERTROPHIC PYLORIC STENOSIS IN INFANCY TREATED WITH METHYL SCOPOLAMINE NITRATE

BY

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The treatment of hypertrophic pyloric stenosis in infancy has provoked many lively discussions and papers during the last 20 years in which the rival claims of medical and surgical treatment have been ably demonstrated. At the same time, increasing interest and skill in diagnosis of the disorders of early infancy have enabled large series of cases to be collected. A review of the literature shows a steadily decreasing mortality rate from this disorder, due not only to improvement in both medical and surgical treatment, but also to the lessened risks of hospital cross infection which have been effected by higher standards of nursing care and hospital accommodation for sick infants.

Still (1924), using medical treatment, reported a mortality of 32·5% in 234 cases. At the Royal Society of Medicine discussion on this subject in 1941, Paterson quoted six deaths in 95 cases treated by Rammstedt's operation at The Hospital for Sick Children, Great Ormond Street, London, in the year 1939. Levi (1941) treated 100 consecutive breast-fed infants surgically with no mortality. Dobbs (1941) successfully treated 31 cases with methyl atropine nitrate, although in a further 12 infants medical treatment failed, and surgery became necessary; Mackay (1941) also reported a series treated with this drug. The consensus of opinion at that time was in favour of surgical treatment, largely owing to the short period in hospital necessary and the quick cure in experienced hands, medical treatment being mainly advocated for babies in good condition who were more than 8 weeks of age when first diagnosed.

More recently in America, Ladd, Ware and Pickett (1946) reported a 5·9% mortality rate in 588 surgical cases, and in this country Wood and Smellie (1951) reported 300 cases treated surgically with four deaths. The series of 100 cases, with 11 deaths in 10 years, reported by Ward-McQuaid and Porritt (1950) is a reminder that even with modern skill surgical treatment can carry quite a considerable mortality rate.

In 1951, when this subject was again discussed at the Royal Society of Medicine, Tallerman reported one death in 41 cases treated with methyl atropine nitrate and 26 surgical cases with five deaths, and Denis Browne (1951) reported 407 unselected cases treated surgically with a 2% mortality rate in London between the years 1943 and 1945. Davison (1951) quoted a 3% mortality rate in the last 500 cases treated in Newcastle-on-Tyne. Dobbs rightly pointed out that the trend of falling mortality for this disorder corresponded closely with that for the total infant population, suggesting that the same factors might well influence mortality rather than specific improvements in medical and surgical treatment. During this discussion emphasis was properly laid on the importance of early diagnosis, and adequate attention to the minute details of infant care whether medical or surgical treatment was employed.

At Bristol Royal Hospital for Sick Children, in the seven years immediately preceding this investigation, there were 267 cases of pyloric stenosis treated by Rammstedt's operation, 12 of which died, a mortality rate of 4·5%. In the years 1946-49 this rate had improved, as in 132 cases there were only three deaths, a mortality rate of 2·3%.

While surgery seems to have been the treatment of choice in most large centres in Britain, medical treatment has continued to evoke interest. In Scandinavia particularly, fresh encouragement was given by Svensgaard (1935) who first advocated the use of methyl atropine nitrate ('eumydrin'). Jacoby (1946) reported the successful treatment of 50 consecutive cases with this drug and emphasized the part played in medical treatment by a restricted feeding regime. Todd (1947) reported a series of 112 cases treated medically in Leicester, in which 12 deaths occurred. He rightly stressed the factor of locality, and that operation, unless carried out by a skilled surgical and anaesthetic team may give considerably less good results than those reported from the large centres.

Nyman (1943; 1944) studied the properties of the atropine-scopolamine group of drugs with a view to finding a suitable anticholinergic compound for use in disorders of the alimentary tract. Scopolamine hydrobromide has in many respects the most powerful anticholinergic action of this group of drugs, but its action on intestinal musculature is only about half that of atropine sulphate, and therapeutic use is limited owing to its powerful central inhibiting action. Increased cholinergic activity of atropine by methylation had already been demonstrated, and Nyman (1944) synthesized a new substance by the transformation of the trivalent nitrogen in scopolamine into methylated pentavalent nitrogen (Fig. 1).

The most important property of this new compound is the elimination of central inhibitory action, although big doses have the same central excitatory effect as atropine and methyl atropine. Investigation of the spasmolytic effect on guinea-pig intestine showed that there appeared to be a selectively increased effect on smooth musculature without the appearance of undue side-effects such as dryness and mydriasis, which is the most important advance compared with the atropine derivatives, and tachycardia was not a noticeable problem. Investigation of methyl scopolamine salts showed that the nitrate was the most effective preparation, probably due to a slower rate of elimination.

This experimental work indicated that the spasmolytic effect on guinea-pig intestine of methyl scopolamine nitrate was five times greater than atropine, and two to three times greater than methyl atropine nitrate. A.B. Pharmacia (Stockholm) manufactured this drug under the trade name of 'skopyl', and it seemed clearly indicated for clinical trial in the treatment of hypertrophic pyloric stenosis of infancy. Elgenmark (1944) first reported the successful treatment of four cases.

Malmberg (1949) reported 136 cases medically treated from 1934 to 1948. The first 77 infants were treated with atropine derivatives, but 23% needed surgery as the response was inadequate; one child died from intercurrent infection. From 1945 to 1948, 'skopyl' was used for 59 cases; one died from gastro-enteritis but none required operation.

In view of Malmberg's claim that 'skopyl' is more efficient, quicker and less dangerous than treatment with atropine or 'eumydrin', and that it has greatly reduced the need for surgery, the present investigation was undertaken to evaluate its use in the treatment of infantile hypertrophic pyloric stenosis.

In assessing the claims of any particular line of treatment, certain questions must be answered: (1) In what proportion of cases does the treatment cure or relieve the disease? (2) Has the treatment any risks or mortality of its own? (3) Does it necessitate the exposure of the patient to any other undesirable risks, and, if so, are these adequately compensated for by the safety and efficiency of the treatment?

A follow-up survey of the patients and a radiological study of a limited number of cases was made to show the changes occurring in the pyloric canal during and after treatment. The findings of these will be reported in a subsequent paper.

Clinical Material

In order that the experimental trial should be carried out on an unselected sample, 117 cases were obtained as follows:

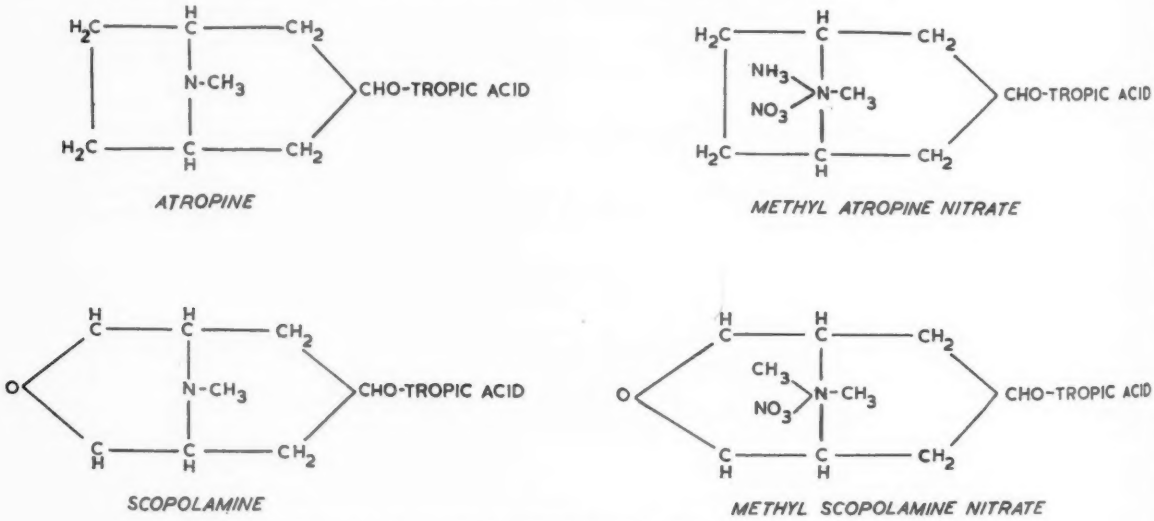

FIG. 1.—Formulae of atropine-scopolamine and methylated compounds (Nyman, 1944).

(1) From March, 1949 to March, 1950, every case irrefutably diagnosed as pyloric stenosis admitted to the Bristol Royal Hospital for Sick Children and to the paediatric department of Southmead Hospital was included in the trial, with the exception of three consecutive cases in April, 1949, for which no 'skopyl' was available.

(2) From March, 1950 to September, 1951, all cases were still included at Southmead Hospital. At Bristol Royal Hospital for Sick Children alternate emergency admissions and all cases seen personally by the author before admission were included, other cases being treated surgically. Since September, 1951, this arrangement also applied to Southmead Hospital.

The criteria for diagnosis were clinical. The two classical physical signs, visible gastric peristalsis and a palpable pyloric tumour were confirmed by at least two experienced observers, and no case was included unless both these signs were present. In cases of doubt, radiology was employed.

Method

All patients were admitted to hospital, and in order that treatment should not be delayed most of the cases were diagnosed before admission, although sometimes a short period of observation was necessary. During the first two years nearly all babies were nursed in wards reserved for infants or neonatal nurseries. At Bristol Royal Hospital for Sick Children there were 6-ft. high glazed screens between the cots, but no separate cubicles were available.

Cubicled wards became available later in both hospitals, thus enabling better nursing techniques to be instituted, so reducing the risks of cross-infection. Simultaneously a new policy was developed whereby the mothers nursed their own children before discharge from hospital, and care was taken to ensure that no infant returned to a home where acute infection was rife among the household. Limited supplies of 'skopyl' during the first year necessitated strict economy in dosage and the retention of patients in hospital for the whole period of treatment. All these factors contributed considerably to the length of stay in hospital of many patients, and therefore it has not been a primary object of the trial to reduce the length of stay to the minimum period necessary to relieve symptoms.

On admission, information was obtained as to the date of onset and severity of vomiting, as judged by the number of vomits per day and a rough estimate of the size. A clinical estimate of the state of hydration was made and parenteral fluids were given if indicated.

In the early cases in this series an attempt was made to continue a normal feeding regime with 'skopyl', 0·1 mg., administered as a tablet dissolved in half a teaspoonful of water by mouth, 15 minutes before feeds, three times daily. (The 'skopyl' drops advocated by Malmberg were not available until later in the trial.) A few babies rapidly ceased vomiting, but experience showed that for the majority a special feeding schedule of the 'ladder' type, as used after Rammstedt's operation, was necessary.

The following is the regime that was eventually adopted:

(1) The stomach is washed out with normal saline.

(2) Five per cent glucose water, or equal parts glucose water and Darrow's solution or saline, is given for the first 24 hours, at two-hourly intervals, starting with drachms ii and increasing by drachms ii at alternate feeds.

(3) If vomiting has ceased at 24 hours, half-strength milk feeds are given alternately with the water feeds. When 2 oz. is reached, the water feeds are omitted and a three- or four-hourly schedule with night feeds, gradually increasing the size of the feeds until $2\frac{1}{2}$ oz./lb. daily is taken, calculated on actual body weight.

(4) Human milk or 'frailac' is used for babies who have been breast fed, premature babies, or those in poor condition. For all other babies, half-cream Cow and Gate dried milk was used, as it was thought that the lessened curd formation in the stomach which would result from using a dried milk with reduced protein might be advantageous. Breast feeding is usually resumed on the third or fourth day of treatment, and other milk feeds are brought up to full strength gradually, according to the tolerance of the baby.

(5) Intragastric feeding by milk drip has been employed in a few very ill or feeble babies.

(6) Methyl scopolamine nitrate, 0·1 mg., is given orally, six times daily 15 minutes before feeds, either as a tablet dissolved in a very small quantity of water, or as drops of alcoholic solution.

(7) If vomiting recurs, the stomach is washed out again, methyl scopolamine nitrate is given by subcutaneous injection, and feeding with watery fluids is started again.

The early cases were retained in hospital until 'skopyl' was discontinued, usually four weeks. Subsequently, cases were treated for a longer period and the dosage was more gradually reduced. As soon as normal feeding was well established, vomiting had entirely ceased, and there was evidence of a steady weight gain, the child was discharged home

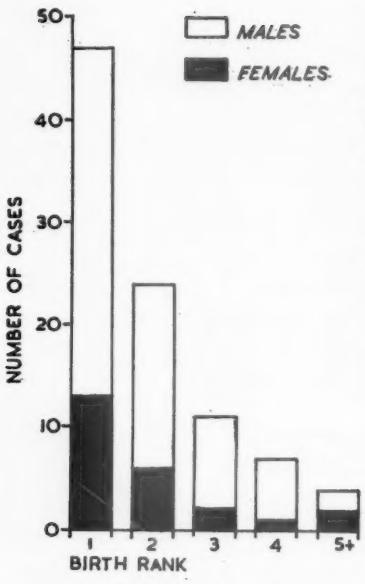

FIG. 2.—Graph showing birth rank.

to continue treatment as an outpatient. If still on treatment, the infants were seen weekly for the first four to six weeks after discharge, otherwise fortnightly till 18 weeks of age and subsequently monthly.

Results

One hundred and seventeen babies with hypertrophic pyloric stenosis were treated with methyl scopolamine nitrate ('skopyl'). There was one death, the tenth case in the series, so that 107 consecutive cases have been treated with no mortality. One case, No. 24, was not making satisfactory progress after 19 days of treatment, and Rammstedt's operation was performed with an uneventful recovery.

Analysis of Case Histories

There were 93 boys and 24 girls, a sex ratio of 3·9 : 1. Fig. 2 shows the place in family of these affected children. One male was the second sibling in his family with this condition, and the maternal uncle of another child had been known to have had Rammstedt's operation for pyloric stenosis in infancy. There was a pair of identical male twins and five other twin infants. The identical twin of one patient was stillborn.

The birth weight distribution of the patients did not differ significantly from that of babies born alive in Bristol during one year of this survey (Fig. 3A and 3B), and included eight premature infants.

Age of Onset. The age at onset of vomiting is shown in Fig. 4. Ten infants vomited in the first week of life sufficiently seriously for medical advice to be sought; three children were seen by the author before the age of 7 days. In none of these cases could a clinical diagnosis of pyloric stenosis be made at that time. Vomiting lessened during the second week, but started again in the third week. Two of these infants continued to vomit intermittently, but were not referred for consultant opinion until the age of 6 weeks when the clinical diagnosis was obvious. Fifty-seven infants vomited before 21 days, and of the whole series, vomiting started in only nine later than seven weeks. One child began to vomit at 82 days, and was admitted to hospital three days later with classical physical signs. The average age of onset of vomiting was 21 days.

The rate of increase of vomiting varied greatly in individual cases. Figs. 4 and 5 show the age at onset of vomiting and the interval that elapsed before treatment was started.

Cases Developing Signs under Observation. Eight children were still in the maternity hospitals when the diagnosis was made. Three were full-term infants who first vomited at 10 to 14 days, and the diagnosis was obvious within three days. The remaining five were premature babies who had been retained in hospital to enable them to reach a

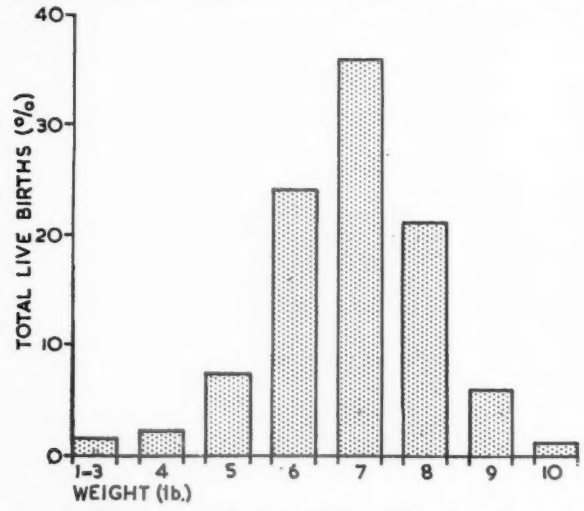

FIG. 3A.—Weight distribution in 6,657 live births in Bristol in 1952.

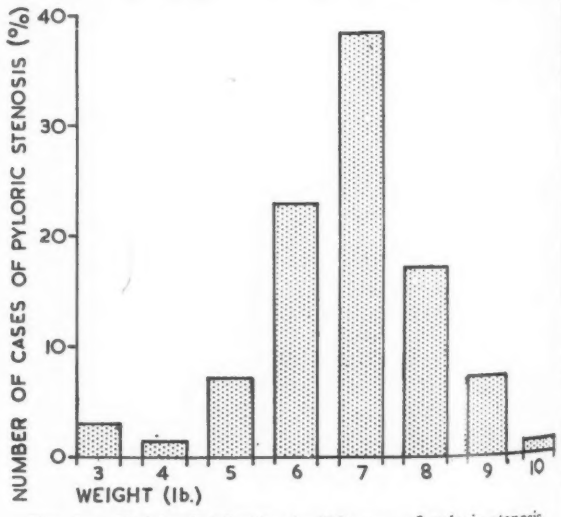

FIG. 3B.—Weight distribution in 117 cases of pyloric stenosis.

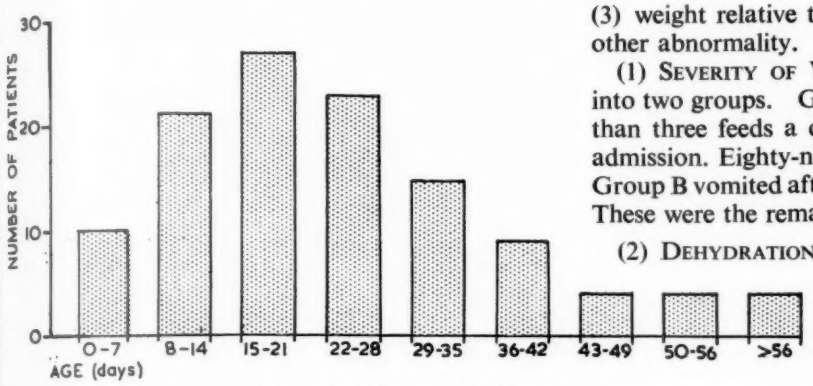

FIG. 4.—Age of onset of vomiting.

satisfactory weight level. The diagnosis was made within 48 hours in three, but the remaining two children vomited less frequently and severely at first, and in one child four weeks elapsed before the pyloric tumour could be definitely palpated. Weight gain stopped abruptly about 48 hours before the diagnosis was confirmed.

The following case history illustrates the occasional difficulty encountered in diagnosis:

B.T., aged 24 days, was a first-born male child (birth weight 7 lb. 4 oz.) admitted with a history of vomiting, occasionally projectile, after some feeds for seven days. No clinical signs of pyloric stenosis could definitely be elicited, although he was observed to vomit intermittently. A barium meal showed no delay in emptying the stomach and no obvious narrowing of the pyloric canal. He remained under observation for two weeks, gained weight steadily and was discharged home. At 7 weeks, he was readmitted with severe vomiting for 24 hours.

There were then physical signs and definite radiological evidence of pyloric stenosis, which responded very satisfactorily to treatment.

Condition on Admission. Cases were assessed according to (1) severity of vomiting, (2) dehydration, (3) weight relative to birth weight, (4) infection or other abnormality.

(1) SEVERITY OF VOMITING. Babies were divided into two groups. Group A had vomited after more than three feeds a day for at least one day before admission. Eighty-nine children were in this group. Group B vomited after three or less feeds in 24 hours. These were the remaining 28 children.

(2) DEHYDRATION. Thirty-eight infants were judged clinically to be dehydrated on admission. Most of these babies had vomited after every feed. Thirty-four received subcutaneous or intravenous fluids during the first few days of treatment. Four children, who relapsed after an initially good response to treatment, received intravenous fluids during treatment of the relapse.

(3) WEIGHT. Cases were divided into five weight groups. Table 1 shows the correlation between the duration of symptoms and weight group on admission.

(4) INFECTION AND OTHER ABNORMALITY. Six children had quite severe infection; oral thrush was present in four patients, one of whom also had purulent conjunctivitis and another had bronchitis. One child was admitted extremely ill with bronchopneumonia; the vomiting was attributed at first to cough, but pyloric stenosis was diagnosed three days after admission. There was one case of purulent rhinitis and conjunctivitis. Two children presented congenital abnormalities: (1) bilateral cleft lip and palate, and (2) mongolism.

Cases of Special Interest. Three cases were included in this series which had received other types of treatment unsuccessfully.

1. M.P., a full-term male infant, developed typical pyloric stenosis at 35 days. Rammstedt's operation was

TABLE 1

CORRELATION BETWEEN DURATION OF SYMPTOMS AND WEIGHT GROUP ON ADMISSION

Interval before Treatment	Weight at Start of Treatment					Severity of Vomiting			
						Group A	Group B		
	Birth Weight	Up to ½ lb. above Birth Weight	More than ½ lb. above Birth Weight	Less than ½ lb. below Birth Weight	More than ½ lb. below Birth Weight	Vomiting Most Feeds	Vomiting 3 or Less Feeds Daily	Dehydration	Parenteral Fluids
Within 3 days	1	2	4	4	2	9	4	3	4
3–7 days	0	4	8	3	6	17	4	9	8
8–10 ,,	2	2	4	2	6	12	4	7	4
11–14 ,,	2	2	8	4	6	17	5	7	7
15–21 ,,	0	2	5	0	4	9	2	3	3
Over 21 days	0	5	17	6	6	25	9	9	8
Total Cases	5	17	46	19	29	89	28	38	34

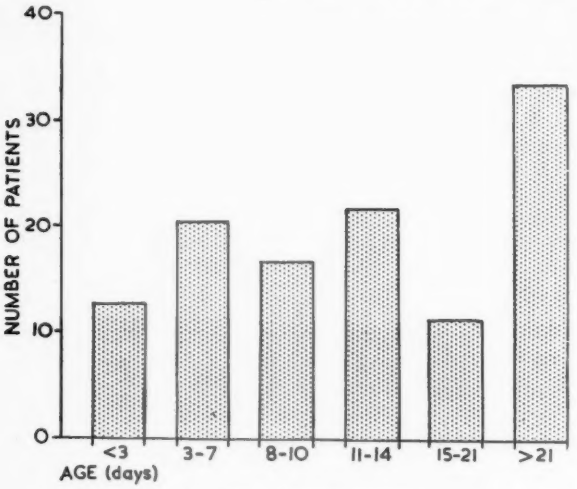

FIG. 5.—Interval before treatment.

performed at a small local hospital outside Bristol. Vomiting continued after operation so that four weeks later he was marasmic. The stomach appeared very large with typical visible peristalis and a very large palpable pyloric tumour. A barium meal confirmed that gastric emptying was greatly delayed and the pyloric canal elongated and threadlike. He responded immediately to treatment with 'skopyl' and made an uninterrupted recovery.

2. V.L. was first seen at 6 months. Birth weight was 8 lb. 12 oz. At 6 weeks typical pyloric stenosis had been diagnosed which had been treated with 0·6% alcoholic solution of 'eumydrin', minims iii, before each feed. This had continued till 4½ months when the child developed gastro-enteritis and was severely ill. She had made very poor progress and still had frequent projectile vomits. At 6 months, weight was 11 lb. 7 oz., typical signs of pyloric stenosis were found, and the diagnosis was confirmed radiologically. She responded rapidly to treatment with 'skopyl'.

3. M.T., a boy, began vomiting in the fifth week and was diagnosed as pyloric stenosis. Treatment with 0·6% alcoholic solution of methyl atropine nitrate was given for seven days, with marked deterioration in the child's condition and persistent vomiting. The response to 'skopyl' was immediate and he started to gain weight at once.

Feeding. Thirty-nine children were fully breast fed on admission to hospital, and 38 were discharged fully breast fed; one was discharged on some complementary feeding. When breast feeding was resumed it was found necessary to test weigh the babies for a few days as occasionally a very large feed was taken which made the child vomit.

Assessment of the Effects of Treatment

Cessation of Vomiting. The speed at which vomiting ceased was considered the most important criterion for judging the effect of treatment. In the early cases of the series, the dosage of methyl scopolamine nitrate was undoubtedly inadequate for most children, and it also seemed necessary to put them on a strict feeding regime for the first few days of treatment. Even so, five early cases on a normal food intake and 'skopyl', 0·1 mg. three times daily, ceased vomiting.

Table 2 shows the rate of cessation of vomiting. It will be noted that 75 infants did not vomit again after treatment was begun (regurgitation of negligible quantities of fluid was ignored), and 19 patients ceased vomiting in 48 hours. Eleven babies vomited intermittently for five days and 12 continued to vomit occasionally after this. These infants usually vomited only once a day or even less frequently, and their condition was such that continuation of treatment seemed justifiable.

During the first year of the trial 55·1% of 49 patients stopped vomiting, and with greater experience of the method, 77·2% of the remaining 68 patients ceased to vomit as soon as treatment had been started.

Weight Progress. A small loss of weight was usual in the first three days of treatment, but 51 infants started to gain within five days. Forty-four children did not start to gain for five days, and 20 only began to gain weight after 10 days, but owing to intermittent vomiting calorie intakes had been kept low according to their tolerance. All the

TABLE 2
INTERVAL BEFORE START OF TREATMENT AND RATE OF CESSATION OF VOMITING

Interval	No Further Vomiting	Vomiting Ceased in 48 Hours	Vomiting Ceased 48 Hours to 5 Days	Continued after 5 Days	Total
Less than 3 days	7	2	1	3	13
3– 7 days	14	3	3	1	21
8–10 ,, ...	7	1	5	3	16
11–14 ,, ...	16	3	0	3	22
15–21 ,, ...	7	2	1	1	11
Over 21 days	24	8	1	1	34
Total cases	75	19	11	12	117

successfully treated cases started to gain weight in less than 21 days from the start of treatment.

Length of Stay in Hospital. As has already been stated it was not a primary object of this trial to reduce the length of stay in hospital to the minimum. Twenty-five children were in hospital for less than 14 days; 27 were discharged in 14 to 21 days, 22 at 21 to 28 days, 14 from 28 to 35 days, and 29 after 35 days. Of the 29 long-stay cases, 18 were treated in the first year of the trial and detained in hospital until the end of drug treatment. Eight of these children had relapses during treatment and were started again. In two cases, gastric drip feeding was used with great benefit. Discharge in one child was delayed by an upper respiratory infection and acute otitis media. Five children were detained in hospital owing to social problems or infection in the home. Other treatment was necessary in four cases, for oesophageal hiatus hernia, cleft lip, and two premature babies too small for discharge.

Duration of Administration of the Drug. During 1949, scarcity of the drug led to early discontinuation in some cases with subsequent relapse. However, treatment for four weeks or less was successful in 10 cases, another three were treated for 28 to 35 days, and four for five to six weeks.

As spontaneous improvement tends to occur in this disorder at about 16 weeks, it was ultimately decided that routine continuation of treatment till about that age would simplify out-patient supervision. The remaining patients were therefore treated for 10 weeks or longer, and the tendency to relapse was eliminated.

Complications. No symptoms or signs attributable to toxic action of the drug were seen, but the oral dosage of 0·6 mg. daily was never exceeded, and half this dose by subcutaneous injection was well tolerated. The only complications therefore were relapse of vomiting and intercurrent illness.

Failure to Suppress Vomiting and Relapses. The only important complication has been inadequate control or relapse of vomiting after cessation for some days. This occurred almost entirely in the first cases treated, and subsequent experience suggests that the dose of 'skopyl' was too small, and insufficient care was taken in regulating the food intake. In more recent cases, if the child was severely dehydrated or much below birth weight, treatment has been begun with subcutaneous injections of methyl scopolamine nitrate, 0·05 mg. six times daily.

A recent case of a severely ill baby who was successfully treated demonstrates this point.

J.B. weighed 5 lb. on admission at 4 weeks old, having lost 2 lb. in weight since birth and with two weeks' history of vomiting. He was dehydrated, very lethargic, with deep jaundice and severe oral thrush. Typical physical signs were present. Subcutaneous fluid was administered to combat dehydration, and 'skopyl' was given by subcutaneous injection of 0·05 mg. six times daily. Vomiting ceased completely and an uninterrupted recovery followed. Frailac feeding was used.

Eight cases in the first year relapsed within a week or two of stopping treatment, but were successfully treated again. In the second year, one baby relapsed who had only received treatment for five weeks. With longer periods of treatment no relapses occurred.

Intercurrent Infection. Two children developed upper respiratory infection in hospital, one was complicated by slight secondary diarrhoea and the other by otitis media. One infant, nursed in an 'open' mixed children's ward, developed gastro-enteritis which responded fairly rapidly to treatment.

Failures

The 24th case in this series responded inadequately after prolonged trial and was treated surgically.

M.S., aged 5 weeks, started vomiting at 2 weeks of age. The birth weight was 7 lb. 10 oz. and admission weight 6 lb. 4 oz. Moderate dehydration was corrected with subcutaneous fluid. 'Skopyl' was given by mouth, 0·1 mg. three times daily, and subsequently by subcutaneous injection. Vomiting did not cease entirely although it lessened in amount, but, as there was no weight gain, on the 19th day it was decided to perform a Rammstedt's operation, which was followed by uninterrupted recovery.

One patient died, the tenth in the series.

J.L. was a first-born male child (birth weight 9 lb. 1 oz.). He was not admitted for 10 days after the onset of vomiting and his weight had by then fallen to 8 lb. 7 oz. There was moderate dehydration, severe thrush, purulent conjunctivitis and rhinitis. Treatment was started with 'skopyl', 0·1 mg. orally three times daily, but this dose was subsequently doubled. Intravenous fluid, 0·43% dextrose with 0·18% saline, was used to overcome dehydration, and human milk feeds were given.

There was initial improvement, but the striking and unusual feature of the case was severe anorexia, necessitating tube feeding. The oral infection cleared but an upper respiratory infection persisted despite antibiotics, and daily stomach wash-outs yielded large quantities of mucopus. The baby's general appearance remained marasmic. Blood electrolytes on two occasions showed no significant disturbance. The sepsis and poor general condition seemed to contraindicate surgery. After three weeks' treatment, vomiting was controlled but anorexia persisted.

Death occurred unexpectedly after four weeks. Acute dehydration developed in the absence of vomiting or

TABLE 3

PREMATURE INFANTS (5 LB. 8 OZ. OR LESS AT BIRTH)

Case No.	Sex	Birth Weight	Age at Onset (days)	Interval before Treatment (days)	Oz. Relative to Birth Weight	Response to Treatment	Remarks
1. B.H.	F	3·5	38	5	+26	No further vomiting	Good progress
2. J.C.	M	3·7	42	2	+16	Vomiting ceased within 48 hours	Treated for retinopathy of prematurity with A.C.T.H.
3. J.S.	M	3·10	24	2	+ 9	1 vomit daily for 4 days	Good progress
4. M.P.	M	4·1	17	1	+ 4	No further vomiting	Good progress
5. J.F.	M	4·11	50	15	+16	No further vomiting	Good progress
6. L.H.	F	5·1	24	28	+ 4	3 vomits in first 6 days	Good progress
7. R.M.	M	5·4	35	1	+24	No further vomiting	Good progress Binovular twin
8. D.T.*	M	5·7	46	11	+42	No further vomiting	Good progress Uniovular twin

* J.T. was the uniovular twin of D.T. (birth weight 6 lb. 2 oz.) and also had the disease. Onset at 65 days, treatment started seven days later with good result.

diarrhoea, and plasma electrolytes three hours before death were normal, although the baby appeared to have an acute diuresis. A necropsy showed typical hypertrophic pyloric stenosis; all other organs were normal.

Discussion

The present series of cases is the largest yet reported of the use of methyl scopolamine nitrate for the treatment of infantile hypertrophic pyloric stenosis. The cases were unselected and included children throughout the normal distribution of birth weights, with all degrees of severity of the disease, some being severely dehydrated. With the exception of two infants, all responded to the treatment, symptoms were relieved and weight gain was satisfactorily re-established.

Lindberg (1946) claimed that since the introduction of this drug the number of cases requiring surgical intervention had been reduced, and the very low toxicity of 'skopyl' was also notable. The present series entirely bears out the Scandinavian experience that most cases of this disease will respond adequately and quickly to treatment, and no toxic symptoms or signs were found in the dosage used. Although the importance of adequate dosage was borne out in the treatment of our early cases, Laursen (1952) reported two deaths in babies attributable to a toxic action of this drug, but his dosage was in excess of that used in this series.

Other accounts of medical treatment using methyl atropine nitrate laid down specific criteria for selecting cases. Jacoby (1946) gave as his indications for surgery in preference to drug treatment the early onset of vomiting and severe dehydration. Todd (1947) suggested as criteria for operation (1) the inefficiency of medical treatment after a trial of seven days, (2) gross dehydration and (3) a birth weight below 6½ lb.

If these criteria are applied to the present series of patients, it is seen that 65% began to vomit before the age of 28 days, but the response of these cases was not significantly different from the older children as judged by rate of cessation of vomiting and start of weight gain. The introduction of hyalase has so aided absorption of fluids given subcutaneously that dehydration can now be much more easily controlled with repeated or prolonged subcutaneous infusion, thus obviating the technical problems raised by the necessity for intravenous infusions. In this series, dehydration was not found to be a contraindication to medical treatment, and of 34 children who were considered to need parenteral fluid, only six were given intravenous infusions. (3) Eight babies in this series were premature according to birth weight (see Table 3), and the average age of onset of vomiting was 35·8 days. The history of the progress of these children is similar to that noted by Henderson *et al.* (1952), but in the present very small series the average age of onset was later than in the full-term infants. All these children made a rapid and uneventful response to treatment, and 15 other children with birth weights of 6½ lb. or less did not present any particular difficulties.

It was thought that length of history might give some indication as to the severity of the disease and likelihood of response to treatment (Fig. 5). It will be seen that in all groups of cases the majority of patients responded quickly to treatment, but of the 50 babies who were treated in less than 10 days from the onset of vomiting, seven (14%) still had some vomiting after five days of treatment. Five of the remaining 67 infants (7%) vomited after five days. This difference is not significant (standard error = 4·5). Table 4 gives the details of these 12 patients who, according to Todd's criteria, might

TABLE 4

INFANTS WHO VOMITED MORE THAN FIVE DAYS

Case No.	Age of Onset (days)	Interval before Start of Vomiting (days)	Birth Weight (lb. oz.)	Weight at Start of Treatment (lb. oz.)	Severity of Vomiting	Dehydration	Remarks
4. J.B. (Male)	16	7	6·12	5·12	A.	Moderate; treated with subcutaneous fluids	Breast fed. Treated for 49 days. Vomiting intermittent for 12 days
7. R.K. (Male)	33	11	6·7	6·14	A.	Severe; intravenous fluids	Vomited occasionally for 13 days. Artificial feeding. Treated for 47 days
8. M.H. (Male)	25	3	7·10	7·8	A.	Severe; intravenous fluids	Artificial feeding. Intermittent vomiting for 8 days. Treated for 49 days.
10. M.L. (Male)	32	10	9·1	8·7	A.	Moderate; intravenous fluids	Vomited intermittently for 21 days. Severe infection. Died
16. S.S. (Male)	28	5	8·1	8·13	A.	Became dehydrated on 11th day; treated with subcutaneous fluid	Relapse of vomiting on 10th day. Breast fed. Treated for 4 weeks
17. D.W. (Male)	13	3	7·6	6·6	A.	Intravenous fluid on 19th day	Relapse on 19th day. Treated for 59 days. Breast fed
20. J.D. (Male)	21	7	7·1	7·11	A.	Moderate	Vomited for first 6 days intermittently. Breast fed. Treated for 60 days
24. J.S. (Female)	14	14	7·10	6·4	A.	Severe; intravenous fluid	Operation on 19th day
39. M.O. (Male)	28	26	6·4	6·13	A.	Moderate; subcutaneous fluid	Vomited for 9 days. Treated for 70 days. Breast fed with complement
56. G.W. (Male)	14	14	8·4	7·11	A.	Severe; intravenous fluid; subcutaneous 'skopyl'	Occasional vomiting for 9 days. Treated for 52 days. Breast fed fully
93. J.M. (Female)	19	3	5·10	5·4	B.	Subcutaneous fluid	Some vomiting for 10 days
94. M.K. (Female)	10	13	6·8	6·0	A.	Moderate; subcutaneous fluid	Some vomiting for 10 days. Also had oesophageal hiatus hernia. Artificial feeding with gastric milk drip for 14 days

all have been submitted to surgery. The only case treated surgically was undoubtedly given too small a dosage of 'skopyl' for some time, and with later experience of the drug would probably have responded adequately. The child who died presents a difficult problem. It has been stated by most authors that infection is a definite indication for medical treatment, but in this infant probably surgery should have been attempted when inadequate response to medical treatment had been clearly demonstrated.

The present series has amply borne out the contention of Jacoby and Todd that a strict feeding regime is necessary.

Does the treatment expose the patient to any other risks? The importance of reducing the length of stay in hospital has always been stressed owing to the risk of cross-infection. In this series, 74% of infants were in hospital for less than 28 days and 21% for less than two weeks. With increased experience of the treatment it seems likely that most cases should be capable of discharge home within a fortnight. No attempt was made to treat any patient entirely at home.

The very low rate of intercurrent infection is evidence of the high standard of nursing technique, and the constant vigilance required to prevent contact with infected children. It is noteworthy that the only case of gastro-enteritis occurred in a baby who was nursed in an open ward occupied by children of all ages. It cannot be demonstrated that on the whole in this series admission to hospital had exposed the children to any undue risks.

Todd rightly emphasized the highly important part played by the nursing staff in the treatment of these cases, and the principle should now be accepted that every baby suffering from this disease requires treatment in a properly staffed and equipped paediatric unit. Under such conditions both surgical and medical treatment give very good results with a low mortality rate.

The present trial demonstrated that methyl scopolamine nitrate given either orally or by subcutaneous injection is a safe and highly effective

drug for medical treatment and can be used efficiently in nearly all cases if supported by a suitable feeding regime and measures to combat dehydration. As no particular factors appeared to influence the response to treatment, Malmberg's suggestion that all cases should be tried on this treatment in the first instance seems to be reasonable.

Summary

The literature on the medical and surgical treatment of hypertrophic pyloric stenosis of infancy during the last 20 years is reviewed.

Results of treatment of 117 unselected cases with methyl scopolamine nitrate are presented. One child required operation after a trial period of medical treatment. There was one death (a mortality rate of 0·8%).

Methyl scopolamine nitrate can be administered by mouth or by subcutaneous injection and no toxic effects were observed in the dosage used.

Response to treatment was usually rapid. Sixty-four per cent of infants ceased vomiting immediately, and 80% in the first 48 hours.

The factors of birth weight, length of history, or presence of dehydration did not seem to bear any relationship to rapidity of response to treatment. Therefore no particular criteria are suggested as contraindications.

A strict regime of feeding with a reduced fluid intake at the start is essential.

The period in hospital can probably be reduced to less than four weeks and less than 14 days in most cases.

The importance of proper accommodation for nursing these patients in isolation and the necessity for an experienced nursing staff are stressed.

It gives me great pleasure to thank Professor A. V. Neale, at whose instigation this trial was carried out and who allowed many of his patients to be included; also the other physicians and surgeons on the staff of Bristol Royal Hospital for Sick Children for their interest and cooperation, particularly during the first year when all cases were included. Magnificent cooperation was given by the nursing staffs of the two hospitals concerned, but particular mention must be made of Senior Staff Nurse P. Jewell at Bristol Royal Hospital for Sick Children, who nursed many of the babies and helped to work out the feeding regime.

Grateful acknowledgment is also made for the gift of the original supplies of 'skopyl' by Pharmacia, of Stockholm, and to Dr. Peter Foster for a small supply.

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CONGENITAL LAXITY OF THE LIGAMENTS WITH HYPOTONIA

BY

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Extreme mobility of the joints is of great advantage to an acrobat, permitting him to assume fascinating postures. When the condition appears in infancy, however, it may be quite alarming, as it may easily be confused with serious organic disease if the features are not known.

There are two basic disturbances in this condition: (1) Abnormal mobility of the bones at the joints, and (2) extreme hypotonia of the muscles. In describing their cases, orthopaedic surgeons have tended to emphasize the former aspects, while physicians have tended to emphasize the latter.

The majority of recorded cases have appeared in the American literature, the first author to draw attention to this anomaly in infancy being Finkelstein, who in 1916 described a 21-month-old child with extreme mobility of all the joints and marked hypotonia. He carefully distinguished the condition from Oppenheim's disease by the fact that there was no gross neurological disturbance in his case, the reflexes were normal and the electrical reactions of the muscles were normal. He called the condition 'joint hypotonia'—an obvious misnomer. Sobel (1926) suggested the term 'essential or primary hypotonia', while Key (1927), Michaels and Searle (1933) and Sturkie (1941) emphasized the 'hypermobility of the joints'. Sutro (1947), on the other hand, described his cases under the title 'Hypermobility of Bone due to "Overlengthened" Capsular and Ligamentous Tissue', thus implying that the anatomical basis of the condition lay primarily in the joint structure rather than in the hypotonic 'overlengthened' muscle and tendon. Lidge (1954) recently described a case under the simple title of 'Hypotonia', while Ford (1952) called it 'Congenital Laxity of the Ligaments (Congenital Atonia)'. For practical purposes I think that 'congenital laxity of the ligaments with hypotonia' covers these cases adequately.

Case Report

I.S. (No. 25925), a boy, was born on December 10, 1953. The patient was referred to the Out-patient Clinic of the Belgrave Hospital for Children by Dr. J. A. Gavin, to whom I am indebted for many of the details of the patient's early history.

The infant was delivered at home and was a full-term, normal delivery, birth weight being 7 lb. He had a strong cry and was of good colour. However, it was noted that he was unusually flabby and tended to slip

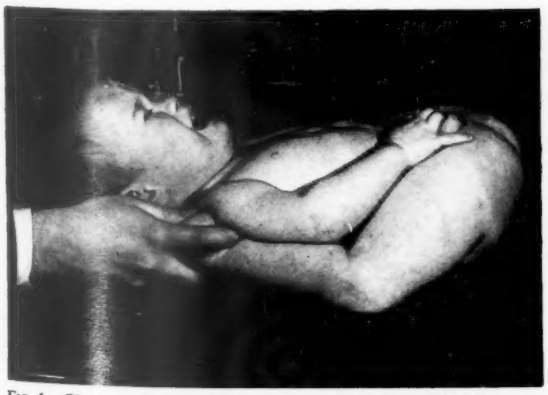

FIG. 1.—Photograph showing extreme mobility of the hip joint. The patient is not in pain, despite the expression on his face. He was hungry and tired.

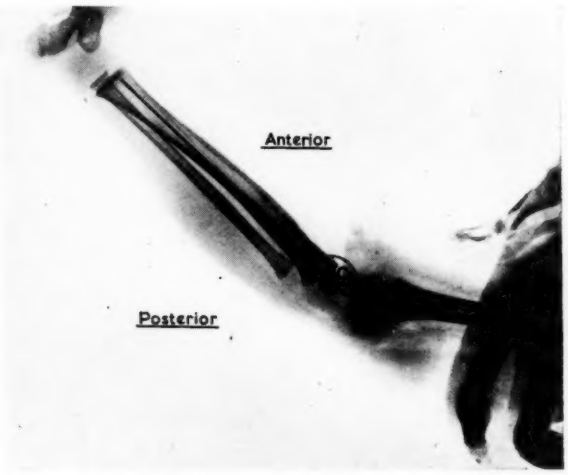

FIG. 2.—Hyperextension at knee-joint through an angle of 30°

FIG. 3.—Marked dorsiflexion of ankle.

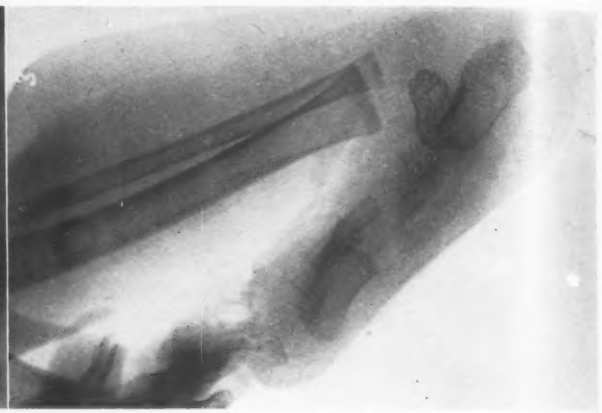

FIG. 3A.—Extreme dorsiflexion of ankle.

through the fingers when lifted up under the armpits. He tended to lie very passively but fed well. He was breast fed for nine months and fully weaned by 10 months of age. He was an only child and it was found that a nephew of his father had a similar condition. Neither of the parents had seen this child, as he lived a considerable distance away.

At the age of 4 months the child was still unable to lift his head and tended to lie very passively on his back. The movements of his eyes showed that he took an active interest in his surroundings. His forehead appeared to be bossed and as both fontanelles were widely patent it was thought that he might have rickets. Large doses of vitamin D were given without effect.

The child was seen for the first time at this hospital at the age of 10 months because of a possible neurological disorder or resistant rickets.

On examination he was found to be a bright-eyed, cooperative, well nourished child who lay passively on the couch and made few movements. The forehead was rounded but there were no stigmata of rickets, mongolism or cretinism. The anterior fontanelle was large and the posterior fontanelle was closed. The skin was healthy. Palpation of the muscles gave the impression that there were no muscle masses at all and that one was palpating fatty tissue only. The abdomen was protuberant.

The patient could sit for a short time with support, but tired rapidly and would slump. There was an abnormal range of movements at all the joints, some of the abnormal postures being illustrated in the radiographs and photographs. Fig. 1 shows the extreme mobility at the hip joint, the movement being painless. Hyperextension of the knee is seen in Fig. 2. Figs. 3 and 4 show the extremes of dorsi- and plantar-flexion at the ankle joint. This mobility is well seen in the radiographs (Figs. 3A and 4A). A photograph of the wrist in full flexion and a radiograph in full extension are also shown (Figs. 5 and 5A). Note particularly the angulation at the metacarpo-phalangeal joint. The absence of pain on extreme angulation of the joints was striking. On lifting the child from the supine position with the examining forearm in the hollow of the lumbar spine, he would double backwards in opisthotonos and made weak attempts to flex the head, knees and hips. The extreme laxity of the joints was most marked at the ankles and wrists which, when passively shaken, behaved like flail joints. Nevertheless, active movements were possible and the child could grasp objects with his hands.

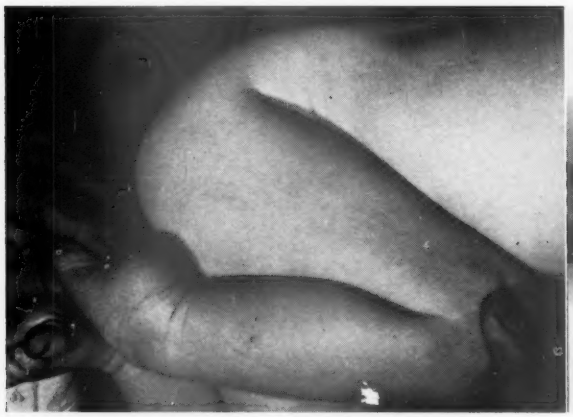

FIG. 4.—Marked plantar flexion of foot.

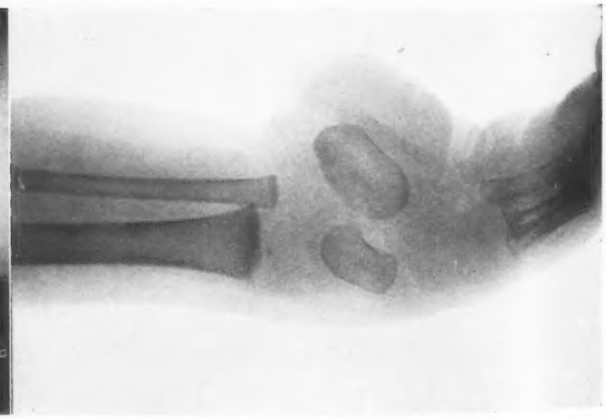

FIG. 4A.—Marked plantar flexion of foot.

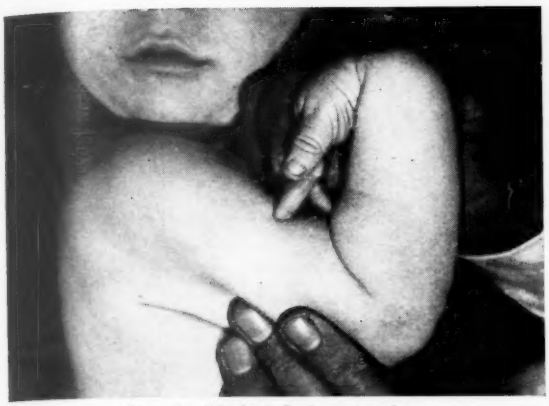

FIG. 5.—Marked flexion at wrist.

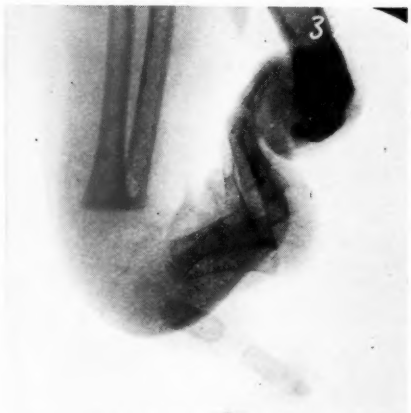

FIG. 5A.—Hyperextension of wrist and metacarpophalangeal joints.

No neurological disorder could be detected, the cranial nerves were intact and the reflexes were all present and normal.

No subluxations were detectable either clinically or radiologically.

Soft-tissue radiographs of the calf muscles showed a normal muscle mass, a useful differentiating feature from amyotonia congenita and Werdnig-Hoffman disease in which atrophy is seen (Figs. 6 and 7).

An electro-diagnostic report from Dr. P. Bauwens, of St. Thomas's Hospital, is as follows:

> 'Stimulation of the main nerve trunks appeared to produce normal reactions in the muscles supplied by the nerves. Electromyographic exploration of the right tibialis anticus did not reveal any spontaneous activity, while on action, provoked by stroking the sole of the foot, a normal complete interference pattern of motor unit origin was noted.'

The patient was seen again two months later at the age of 1 year and showed a remarkable improvement in activity. The mother complained that he had become 'too active' so that it was practically impossible to dress him. He would twist and squirm and was hardly still for a minute. He could pull himself to an upright position, but, owing to the laxity of the ankle joint, could not take steps. On standing, the foot would assume either an everted or inverted position, and, despite its awkwardness, the position was completely painless.

Discussion

The aetiology of congenital laxity of the ligaments is unknown. The condition is probably congenital, and Finkelstein noted in his case that a grandmother, two uncles, and the mother of the child had had flail joints in infancy which improved in adolescence. In Jahss's (1919) case the paternal grandfather and an uncle had had similar trouble in infancy. Sobel (1926), who has collected the largest series in the literature, noted that other members of the family were affected in four cases. Key (1927) described a family with hypermobile joints involving the father and four sons, whereas the five daughters were normal. It is of interest, however, that all four sons had club-feet in addition, the only joints in the body that were not hypermobile. Key thought that this family illustrated an example of a sex-linked hereditary characteristic. However, Sturkie (1941) reported a family in which all the offspring in two generations (nine cases in all) had hypermobility of the joints to greater or lesser degree. Of these, three

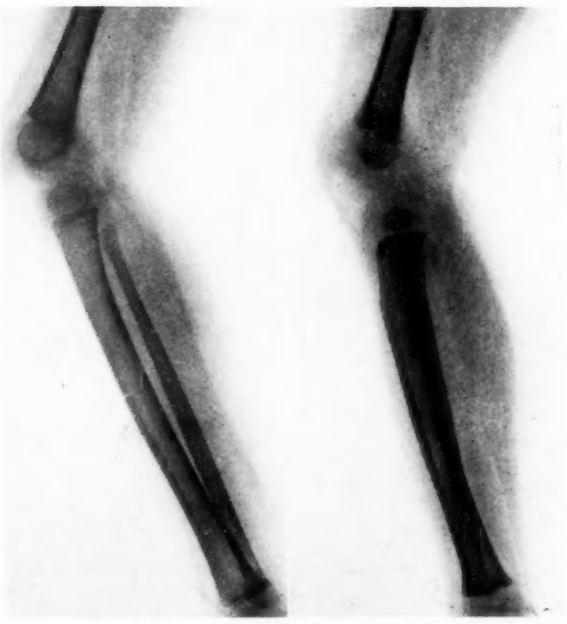

FIG. 7. FIG. 6.

FIG. 6.—Soft tissue radiograph to show normal muscle mass.
FIG. 7.—Case of Werdnig-Hoffman disease to show atrophy of muscle mass.

TABLE 1
SUMMARY OF CASES REPORTED IN THE LITERATURE

Author	No. of Cases Generalized	Local Forms	Age	Sex
Finkelstein (1916)	1	—	21 m.	F.
Jahss (1919)	1	—	17 m.	M.
Sobel* (1926)	17	28	5 cases less than 1 year 23 ,, 1-2 years 7 ,, 2-3 years 10 ,, 3-11 years	22 M., 23 F.
Key (1927)	2	—	4 and 6 yr.	M.
Michaels and Searle (1933)	1	—	Adolescent	M.
Sturkie (1941)	9	4	Not stated	9 F., 4 M.
Sutro (1947)	5	—	Young adults	
Ford (1952)	2	—	2 and 7 yr.	F.
Lidge (1954)	1	—	16 m.	F.
	39	32		

* Of Sobel's 45 cases, 17 appear to be generalized and severe, and would seem to be comparable to the case that we are describing. His other cases were described as moderate or mild, but he gives no criteria for the distinction.

were males and six females. The mother, incidentally, had hypermobility limited to the fingers and thumb only, thus a localized and a generalized form of the condition can occur in the same family. In the case reported here, it is noted that a first cousin is reported to have hypermobile joints.

Clearly the transmission of the hereditary character is irregular and there is considerable variation in expression. Its transmission cannot be explained in terms of Mendelian recessive inheritance.

Of 71 cases of both the generalized and localized forms in which the sex is mentioned, 35 were male and 36 female. These cases are summarized in Table 1. Adults as well as infants are included.

Prognosis and Complications.—The prognosis is excellent, the condition improving as the child grows older. There may be a tendency to constipation because of atonic abdominal musculature, but this was not so in our case. Sutro (1947) described recurrent effusions into the joints in five cases. In three cases both knees were involved and in two cases the ankles.

Hypotonia with laxity of the ligaments may occur in many disorders, and the following classification is offered from the point of view of differential diagnosis.

(1) *Primary hypotonia*
Congenital laxity of the ligaments.
1. Generalized type.
2. Localized type.

(2) *Secondary hypotonia*
1. Disorders of the central nervous system.
(*a*) Cortical degenerations, maldevelopments, and malformations.
(*b*) Amaurotic family idiocy.
(*c*) Congenital atonic diplegia (hypotonic cerebral palsy).
(*d*) Injury to the spinal cord.
2. Disorders of the anterior horn cell.
(*a*) Amyotonia congenita (Oppenheim's disease).
(*b*) Werdnig-Hoffman disease.
(*c*) Acute ascending polyneuritis.
3. Atonic type of chorea.
4. Sedative drugs.
(3) *Muscle dystrophies and atrophies*
(4) *Endocrine disorders such as hypothyroidism*
(5) *Nutritional disorders*
1. Chronic wasting disorders.
(*a*) Infections.
(*b*) Malignancy.
(*c*) Chronic undernutrition from any cause.
(*d*) Rickets.
(6) *Mongolism*
(7) *Ehlers-Danlos syndrome*
(8) *Brittle bone disease with blue sclera*

Congenital laxity of the ligaments is easily differentiated if the following points are remembered: (1) There may be a family history of the disorder. (2) The intelligence is unimpaired. (3) Muscle power is normal though the tone is poor. (4) There is hypermobility of the joints which varies in degree and may be localized to one or more joints. (5) The reflexes are normal. (6) Electrical studies are normal. (7) Soft tissue radiographs of the limbs show a normal muscle mass.

Summary

A case of congenital laxity of the ligaments with hypotonia is presented and the literature is briefly reviewed.

The diagnostic features are emphasized.

I wish to thank Dr. A. Doyne Bell for his help and interest in this case and for permitting me to use the photograph of the child with Werdnig-Hoffman disease. I also wish to thank Mr. W. Smith, Photographic Department, King's College Hospital, for his assistance.

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MANDIBULO-FACIAL DYSOSTOSIS (TREACHER COLLINS SYNDROME)

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 3, 1955)

Mandibulo-facial dysostosis has been described with increasing frequency in recent years. Once known it is readily recognized and may be more common than is sometimes imagined.

We describe in this article a case seen in a newly-born infant who died at the age of 2½ months and in whom careful dissections were made of the facial region.

The infant (A.R., 456/1954) was admitted to the Royal Aberdeen Hospital for Sick Children at the age of 2 weeks because he failed to feed easily. The infant was born of a healthy father and mother; the father had been operated on for harelip in childhood; there was a brother of 3 years who was alive and well. No history of any abnormality suggestive of dysostosis was elicited. The infant was born at full-time, weighed 5 lb. 11 oz., and breathed well after birth. He was fed from the beginning with the bottle on half-cream National dried milk. In the second week the child began to feed with difficulty. He would take several drachms of his feed, then fall asleep; there was no vomiting and the bowels moved well. The child at 2 weeks weighed 5 lb. 7 oz.

No abnormalities were found about the heart or lungs. No masses were felt in the abdomen. On admission it was noted that the baby was a 'bird-like creature with rather curious eyes and a receding chin'; the nostrils were somewhat small; there was hypoplasia of the malar bones; the ears were rather low set with some failure of cartilage development, and appeared too big; the tongue seemed a little large and was held towards the back of the mouth. The eyes slanted downwards at the outer ends; there was bending of the lower canthus at the junction of its inner two-thirds and outer third; the eyelashes in the upper lid and in the outer third of the lower lid were normal; they were rather scanty in the medial two-thirds of each lower lid. The appearances of the infant are seen in Figs. 1 and 2. The arms and legs moved well. The palate was high-arched. The following were the body measurements:

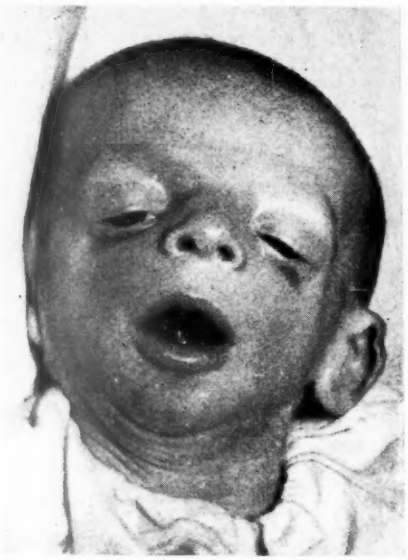

FIG. 1.

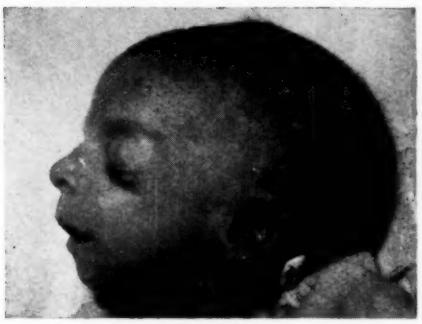

FIG. 2.

Head circumference	350 mm.
Maximum head length	117 mm.
Maximum head breadth	100 mm.
Face length	54 mm.
Face breadth	54 mm.
Nasion-alveolus	37 mm.
Chin-occiput	129 mm.
Chin-vertex	124 mm.
Standing height	475 mm.

Sitting height		350 mm.
Biacromial width		132 mm.
Bitrochanteric width		83 mm.
Fontanelle	Anteroposterior	25 mm.
	Coronal	30 mm.
Palpebral fissure		20 mm.
Ear length		R. 35 mm., L. 33 mm.
Ear breadth		R. 23 mm., L. 22 mm.

Radiographic examination of the skull added nothing to our knowledge of the bony state; there was poor suction of an opaque meal. The oesophagus and fundus of the stomach were normal in outline.

Feeding continued to be difficult and attempts to feed by different types of teat and by spoon were also unsuccessful, so that the infant had to be fed by catheter. The infant appeared to suck but the milk just dribbled out of the mouth. This difficulty continued for a month and then quite suddenly feeding by bottle, which had been constantly attempted, began to be successful, although some milk was constantly lost through apparent

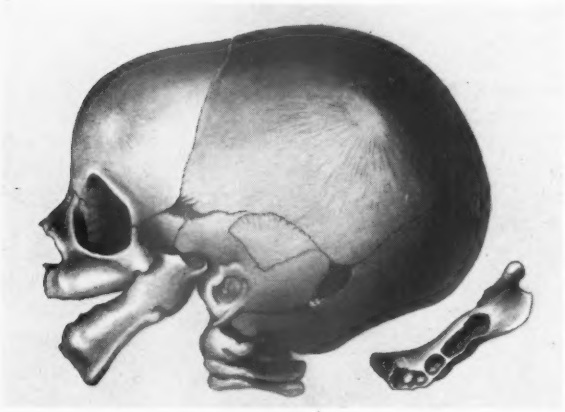

FIG. 3.

inability to swallow properly. In spite of continued attempts to keep him on a feed containing the right amount of calories, he failed to gain weight. An occasional cyanotic attack occurred, and he died at the age of 10 weeks.

A post-mortem examination showed that the body was that of a poorly nourished male child. The brain was of normal size and showed no notable external abnormality; the lungs showed extensive patchy basal collapse with a few areas of consolidation; there was no evidence of inhaled material in the trachea or main bronchi. The pericardial sac and the heart were normal; liver and spleen and intestinal tract were normal; there was no lesion in the gall bladder, pancreas, adrenals or kidneys; the ureters were patent and the bladder normal in size.

The head and neck were fully dissected. Abnormalities similar on both sides were revealed. The zygomatic bone and zygomatic process of the temporal bone were absent (Fig. 3), but the maxilla, as well as completing the margin of the orbit, also provided a postero-lateral projection for the upper attachment of the masseter. It did, however, allow the lower orbital margin to fall away laterally, thereby causing obliquity of the palpebral fissure. The squamous temporal bone was smaller than normal, the deficiency being made up by the surrounding bones and by a small extra plaque between the temporal and the parietal bones. The head of the mandible, elongated antero-posteriorly instead of transversely, was separated from a shallow articular fossa by a normal cartilaginous articular disc; there was no articular eminence; the coronoid process of the mandible was everted while the body was foreshortened and receding.

Within the middle-ear, the incus and stapes were absent, but the middle-ear cavity and internal ear were normal.

There was no parotid gland.

The musculature of the face and head was nowhere deficient; indeed, it was unusually well developed, there being many extra muscle bundles in the facio-platysmal sheet and a tendency for the individual muscles in the masticatory group to become confluent.

The maxillary artery (Fig. 4), after supplying normal

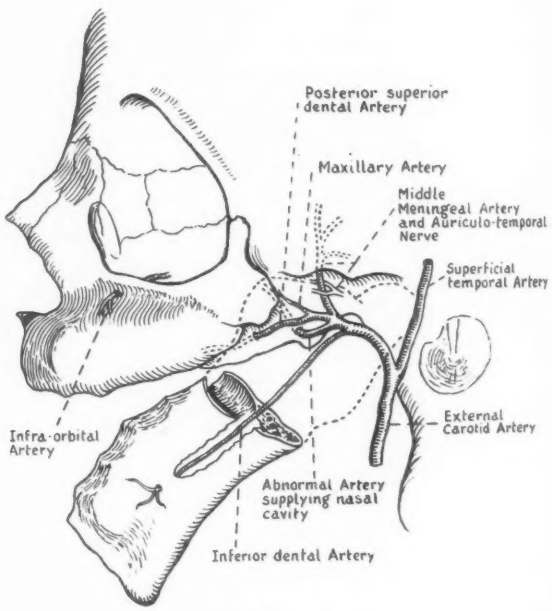

FIG. 4.

inferior dental, posterior superior dental and middle meningeal branches, petered out before it reached the pterygo-maxillary fissure. The lower surface of the palate was supplied by the posterior superior dental vessel, while the nasal cavity received blood from a vessel which arose from the maxillary artery near the origin of the inferior dental artery, ran along the lower border of the lateral pterygoid muscle, entered the pterygo-palatine fossa from behind and finally ran up to and through the sphenopalatine foramen into the nose. The infra-orbital

artery was a branch of the ophthalmic artery. The middle meningeal artery (Figs. 4 and 5), after it entered the skull and before it divided into its two branches, produced a vessel which ran backwards and medially as if it were reaching out for the internal carotid artery, but faded out behind the mandibular nerve.

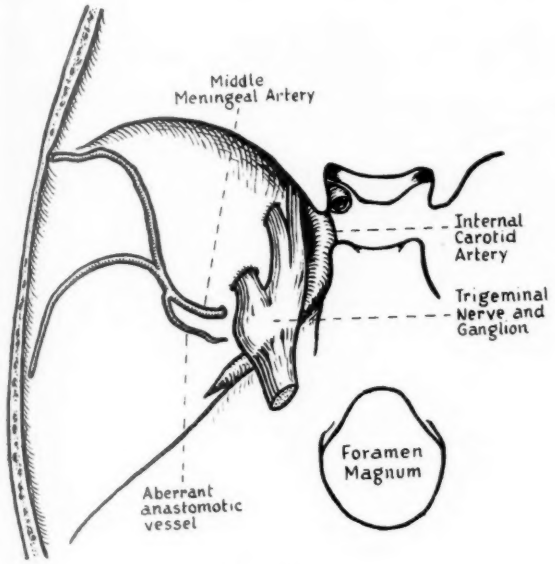

FIG. 5.

Discussion

After Treacher Collins (1900) described two cases showing notching of the lower eyelids associated with defective development of the malar bones, these features were regarded as the essential characteristics of the Treacher Collins syndrome; but it is now realized that many other features such as abnormalities of the mandible and of the ear may be safely included under this title and that the slight anti-mongoloid obliquity of the palpebral fissures, occurring alone in a patient and causing no comment whatsoever, is the minimal clinical manifestation of the same syndrome (Franceschetti and Klein, 1949). After reviewing many of the published cases and describing several others, these authors recognized, as did Mann and Kilner (1943), that the essential lesion was a hereditary maldevelopment of the maxillary process and mandibular arch, and with the data gleaned from clinical and *x*-ray examination, concluded that the cause of this congenital abnormality was 'an inhibitory process occurring towards the seventh week of the embryonic life and affecting the facial bones deriving from the first visceral arch'. They assumed the aetiology to be 'a disturbance of the organization center'.

Hövels (1953a), in a more extensive survey of the literature, graded the recorded cases to form a series, from the simplest form, showing only obliquity of the palpebral fissures, to the most extensive, which included deformations such as agnathia. His attempts (Hövels, 1953b) to find the cause of the abnormality were based on the work of authors such as Hörstadius (1950) who found that the visceral arches were derived in their entirety from the rostral end of the neural crest where areas could be mapped out corresponding to these derivatives. Extirpation of these areas resulted in deficiencies in or the absence of the corresponding arches. Hövels maintained that some defect in the neural crest area responsible for the first visceral arch produced the structural abnormalities of the Treacher Collins syndrome.

This theory, however, will not withstand critical examination. For example, the most frequently affected part of the face is the zygomatic bone which is the proximal part of the maxillary process; if, as Hövels suggests, it were predetermined within the neural crest that there was to be no zygomatic bone, then surely the maxillary process would not be long enough to meet and fuse with the nasal processes. Yet they do; there is no cleft palate, harelip, or interference with the naso-lacrimal duct. The observations obtained clinically and radiologically must be supplemented by the detailed anatomy of the deeper tissues in the region of the abnormality before theories as to its origin are put forward. This has been difficult because the syndrome is quite compatible with life and only occasionally can a case be thoroughly investigated. Lockhart (1929), who first dissected the abnormality, did not correlate his findings with any clinical abnormality, and consequently his article has been overlooked as a source of information on the anatomy of the syndrome. He drew attention to the association of absence of the zygoma with abnormalities in the middle ear and with minor alterations in the muscles of mastication. Even in Hövels' work there is no mention of the condition having been dissected. It is obvious when the abnormalities in the arteries supplying the tissues derived from the maxillary process are considered that this portion of the first visceral arch suffered from a temporary deficiency in its blood supply by occlusion or failure of the maxillary artery at an early age. However, while the zygomatic bone had no alternative means of nourishment at the critical stage of its ossification and therefore did not develop, the maxilla borrowed a blood supply from the internal carotid artery through the ophthalmic artery to tide it over until a secondary source was available from the root of the maxillary artery.

According to Keibel and Mall (1910-12), the

normal development of the arteries derived from the first aortic arch is as follows (Fig. 6): Three arteries are produced from the first aortic arch: (1) the supra-orbital, later to become the middle meningeal artery, (2) the infra-orbital representing the maxillary and (3) the mandibular or inferior dental. With

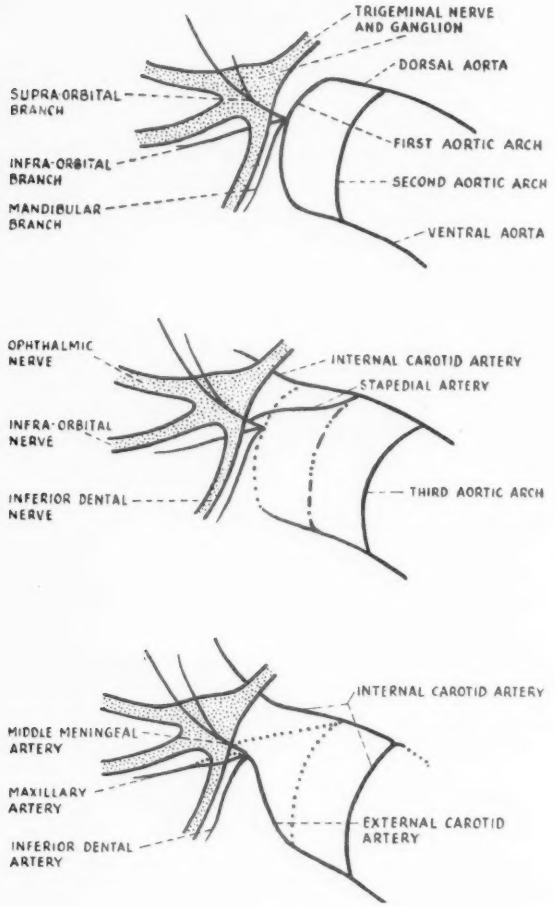

FIG. 6.

associated with the absence of the stapedial than for either of the other two first arch vessels. Could the development of these vessels not be as shown in Fig. 7? Instead of the supra-orbital, infra-orbital and mandibular vessels arising fanwise from a single point, let them arise separately; and let the

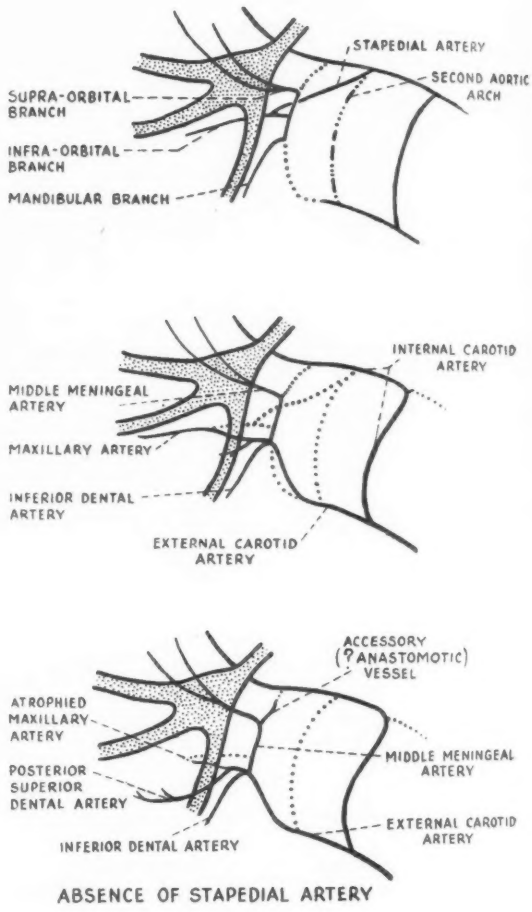

FIG. 7.

the disappearance of the first arch, these three vessels are all maintained by the stapedial artery, a short-lived vessel in the human embryo passing through the stapes, supplying the structures derived from the posterior end of the second visceral arch, and affixing itself to the stem of the supra-orbital artery. When the external carotid artery develops it takes over these three vessels again and the stapedial artery disappears. The two vessels whose absence is involved in the production of the Treacher Collins syndrome are the stapedial and infra-orbital arteries, yet according to the foregoing description there is no more reason for the infra-orbital vessel being infra-orbital artery, since it originally runs deep to the mandibular nerve, be the vessel which receives the stapedial artery and depends on it to a greater extent than do the others for its survival. Without the help of the stapedial artery the middle meningeal artery could still continue to function by retaining its connexion with the dorsal aorta. This is significant when it is remembered that the specimen described here had an aberrant vessel from the middle meningeal artery which could have anastomosed with the internal carotid artery at one time round the back of the mandibular nerve. The mandibular artery could likewise survive from its

connexion with the ventral aorta or the developing external carotid. In addition to describing what is the more probable sequence of events in the development of the vessels in this region, we can also show that there is still in the adult a remnant of the first aortic arch, namely, that part of the middle meningeal artery between its origin from the maxillary and a point near its bifurcation. That small piece of first aortic arch between the infra-orbital and mandibular arteries is transferred to the middle meningeal artery as well when the infra-orbital forms its anastomotic loop around the mandibular nerve to lie superficial to it as in the adult.

It seems, then, that the original lesion in the Treacher Collins syndrome lies with the stapedial artery; its absence will give defects of the stapes and incus and maldevelopment of the first arch vessels usually involving but not necessarily restricted to the maxillary: failure of the inferior dental to retain or find an auxillary source of supply will give concomitant abnormalities of the mandible. The possibility of a normal stapedial capable of supplying the posterior end of the second visceral arch and no more will account for the defects of bones and soft tissues being confined to the face. We can in this way account for all recorded abnormalities constituting the Treacher Collins syndrome, however severe, or however variable, and further we can point to the sixth week of intra-uterine life as being the age for the inception of the abnormality, i.e. immediately after the formation of the primitive face.

Summary

A typical case of the Treacher Collins syndrome (mandibulo-facial dysostosis) is described with the clinical features and the abnormal details of its anatomy.

A fresh suggestion regarding the cause of the abnormality is put forward, based chiefly on the arterial abnormalities present in this case, viz. that a defect of the stapedial artery causes maldevelopment not only in its own field of supply but also in the region of the first visceral arch whose vessels the stapedial artery normally supports during the critical phase between the disappearance of the first aortic arch and the full development of the external carotid artery, just after the formation of the primitive face.

The normal development of the arteries in and near the first visceral arch is reconsidered and modified.

We are indebted to Professor R. D. Lockhart for his interest and advice during the investigation, to Mr. W. Cruickshank for the illustrations and to Mr. R. G. M. Drummond for the photographs.

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TERATOMA OF THE TONSIL CAUSING RESPIRATORY OBSTRUCTION IN THE NEWBORN

BY

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From the Royal Infirmary, Preston

(RECEIVED FOR PUBLICATION JANUARY 12, 1955)

A teratoma, by definition, is a true tumour or neoplasm composed of multiple tissues of kinds foreign to the part in which it arises. In a series of 82 cases Willis (1953) quotes the following sites of origin: ovary, 50, and testes 19, the remainder being epididymal, retroperitoneal, pre-sacral, anterior mediastinal, intrapericardial and cerebral. A careful search of the literature failed to reveal a case where a teratoma had arisen in the tonsillar fossa.

Clinical History

The case reported here was in a newborn infant. Mrs. O.C., aged 31 years, a third-gravida, after a normal labour of 8 hours 50 minutes, was delivered of a full-term female child weighing 6 lb. 9 oz. There had been two previous normal pregnancies which had produced normal children and there was nothing relevant to the present case in the family history.

At birth the child was in a state of asphyxia pallida and, although large amounts of mucus were extracted, respiration remained laboured and difficult: a provisional diagnosis of atelectasis was made. Placed in an atmosphere of oxygen and 7% CO_2 the infant responded slowly and there was some improvement in her colour but breathing was still difficult.

As no further improvement took place it was decided to make a more thorough examination, and on inspection a tumour was seen to be protruding from the posterior surface of the left anterior pillar of the tonsil: the growth was almost entirely obstructing the pharynx. The consultant E.N.T. surgeon of Preston Royal Infirmary thereupon took over the case. He made a tentative diagnosis of sarcoma of the tonsil and took a small biopsy from the tumour.

The infant's condition deteriorated and respiration became almost impossible, but, after emergency enucleation of the tumour mass with a tonsil guillotine breathing was much easier.

After the operation vitamin K and prophylactic penicillin were given but haemorrhage was troublesome. The infant's general condition was too poor to allow the giving of an anaesthetic to secure haemostasis. However, the bleeding was eventually controlled by the use of thrombin drops and the total blood loss was estimated at 4 oz.

After the infant's return to the oxygen tent respiration became increasingly rapid, the rectal temperature rose to 105° F. and the child had cyanotic attacks which were treated with nickethamide. The attacks continued and the baby died some 36 hours after the operation.

Necropsy. On internal examination the main findings were in the respiratory tract. The left tonsil had been removed before death. The fossa was engorged with blood and contained fragments of whitish tissue which were removed. The larynx and trachea were congested and both lungs were enlarged, reddish purple, and their substance showed acute haemorrhagic bronchopneumonia. The right side of the heart was dilated and engorged with blood but otherwise the organ was anatomically normal.

The abdominal organs showed some congestion of the liver but no abnormality elsewhere. The meninges were congested and the brain substance showed no abnormality. The anatomical cause of death was acute haemorrhagic bronchopneumonia.

Pathology. Dr. A. A. Miller reported that the mass removed at operation consisted of one tonsil with two polypi projecting from the external surfaces: the larger polypus measured 15 × 10 mm., and the smaller one 10 × 3 mm. The tonsil measured 20 × 10 × 15 mm., appeared nodular, and on section showed bony, cartilagenous and other white tissues.

Histological examination showed a disorderly mixture of cartilage, cancellous bone, plain and striated muscle, neuro-epithelium, and renal, cerebral and adipose tissues, together with clumped masses of cells which include lymphocytes, plasma cells, eosinophils and multinucleate giant cells (Figs. 2-4). This was a teratoma (Fig. 1).

Our thanks are due to Mr. Tod and Mr. Corbet, consultant gynaecologists, to Mr. Kersley, consultant E.N.T. surgeon, for permission to publish this case, to Dr. A. A. Miller, consultant pathologist for the post-mortem and histological examinations and for looking over the text, and to Mr. F. Ramsden for the photomicrographs.

Reference

Willis, R. A. (1953). *Pathology of Tumours*, 2nd ed. London.

FIG. 1.—Photograph of teratoma of the tonsil. × 3.

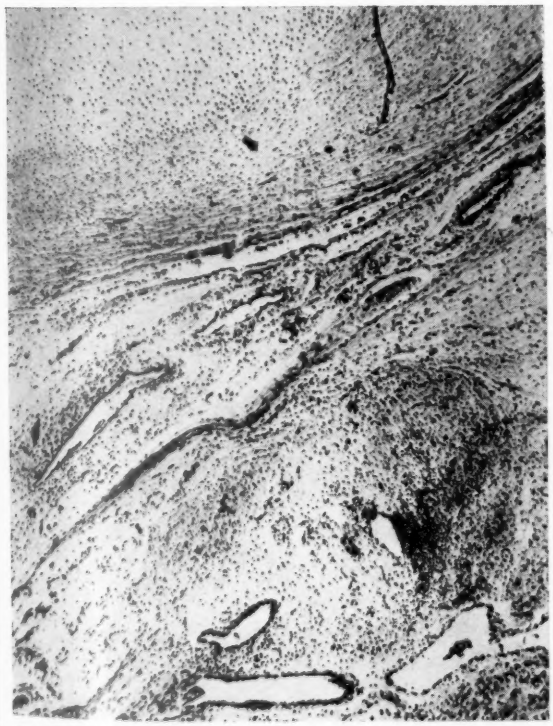

FIG. 2.—Section showing cartilage and connective tissue with epithelial lined spaces. Haematoxylin and eosin. × 60.

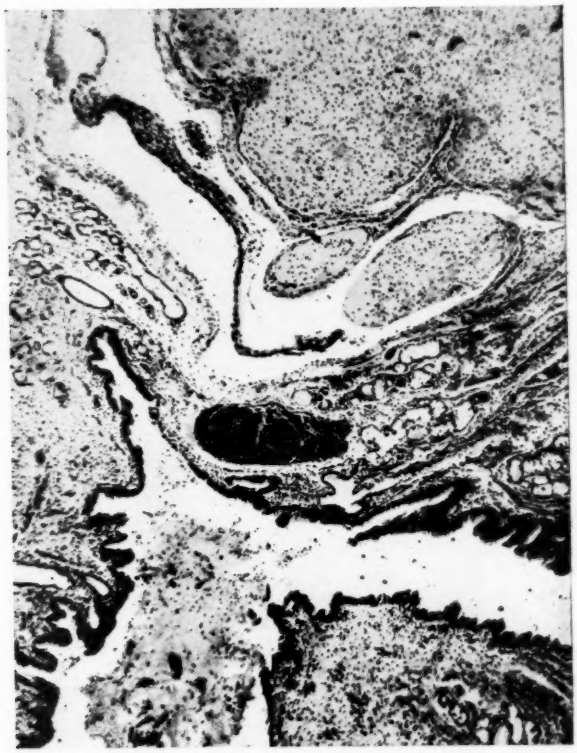

FIG. 3.—Section shows cartilage, mucus glands, lymphoid tissue and neuroepithelium. Haematoxylin and eosin. × 60.

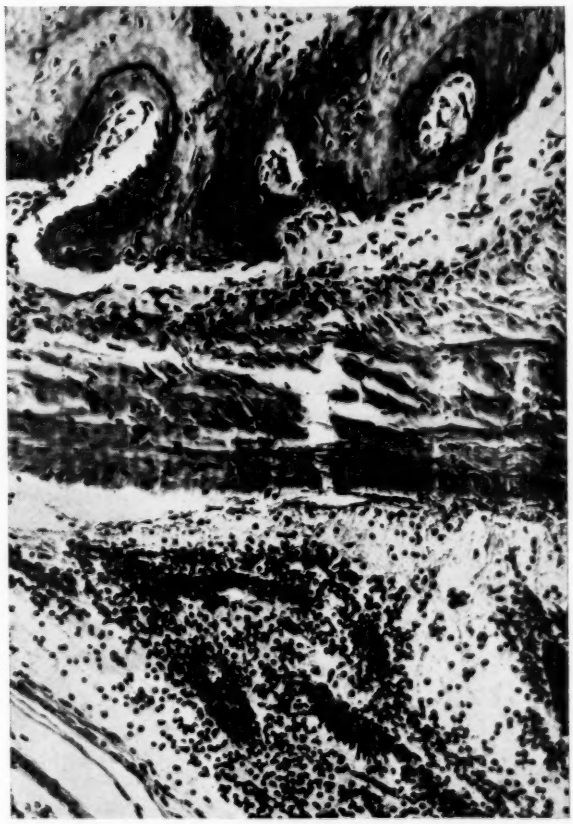

FIG. 4.—A high-power view showing cancellous bone, striated muscle and a mass of lymphocytes. Haematoxylin and eosin. × 120.

BOOK REVIEWS

Atemübungen mit Kindern. By I. MÜLLER-GIES and CHR. LICHTENBERG; Foreword by B. de Rudder. (Pp. 32; 25 illustrations. DM. 3.90.) Stuttgart: Georg Thieme Verlag. 1955.

This booklet is apparently one of three, the others being on foot and postural exercises.

The emphasis is on rhythmical movements. Whilst avoiding discussion of the condition in front of the children, the teacher sees that the movements are carried out correctly each day. It would appear that asthma and many other chest conditions are treated in the same way. The children are exercised for 15 minutes and then given a rest period, lying flat and quiet.

The booklet is divided into sections describing exercises while lying, sitting, etc., but does not apparently give any indication of whether the exercises are taken in series or whether exercises are started lying down and then progress to sitting.

On the whole the instructions are not as good as those issued by the leading British hospitals, and the standard and type of rhythmical exercises are below those taught by educational gymnasts in this country. However, there are a few interesting variations on exercises used in England and it is worth studying these.

Textbook of Paediatrics. Sixth edition. Edited by WALDO E. NELSON, with the collaboration of seventy contributors. (Pp. xviii+1,581; 438 figures. 75s.) London and Philadelphia: W. B. Saunders Company. 1954.

The quality of this comprehensive textbook of paediatrics, now appearing in its sixth edition under the sole editorship of Waldo Nelson, lies in its emphasis on the scientific basis of medicine. Each section opens with long paragraphs of anatomical, physiological and biochemical considerations, against which are contrasted pathological and clinical descriptions, in turn followed by sections on treatment as far as possible based on a rational application of modern therapeutics. With each new edition this tendency has progressed step by step and reflects the fundamental changes in medical thought over the last quarter of a century.

The beautiful clinical descriptions of disease beloved of and so well done by the older generation of writers, inevitably go by the board; but there are a few conditions in this book in which the treatment of the clinical picture has been unnecessarily niggardly and even faulty. Nephrocalcinosis, for instance, considered as a disorder of bones and a problem in renal tubular physiology, is unrecognizable as the syndrome of either Lightwood or Albright; and the condition in this country most often referred to as hiatus hernia is clearly described and obviously taken to be a short oesophagus. With occasional exceptions the subject matter is reasonably up to date, the time lag being indicated by the absence, in a book the preface of which is dated August, 1954, of any mention of gluten.

There are, as before, numerous excellent photographs and pictures as well as copious, comprehensive, only occasionally incomprehensible, plans and charts, and an almost embarrassing quantity of statistical information. It has always seemed to the reviewer a prolific use of 14 valuable pages in the chapter on growth and development to table in seven different percentiles figures for heights in centimetres and inches, and weights in kilos and pounds for both sexes and for all ages from birth to eighteen months at three-monthly, and to 18 years at six-monthly intervals—some 2,296 figures—as well as those for head, chest and abdominal circumference in the same lavish detail.

Such criticism cannot detract from the general excellence of this well-known textbook. The 15-page appendix contains a host of information on normal blood and C.S.F. values, composition of therapeutic solutions, food values and conversion tables, whilst the 62-page, three-column index is ample and accurate.

The paper and printing are only moderate in quality which, with the book's deservedly wide circulation, accounts for its moderate price; at 75s. it must be considered one of the best values for money.

Kwashiorkor. By H. C. TROWELL, J. N. P. DAVIES and R. F. A. DEAN. (Pp. xii+308, illustrated. 50s.) London: Edward Arnold. 1954.

To the reviewer of this book the subject is entirely new. To be critical of its contents is therefore difficult, but it has made instructive and at times fascinating reading. It is a report of a physician, pathologist, research worker and paediatrician on a nutritional problem of world wide distribution and importance which they have studied in Makerere College, Kampala, Uganda.

They believe that kwashiorkor is a protein deficiency disease which can be treated and prevented by milk protein, and they marshall the evidence in sections on the history of the disease, its clinical picture, its pathology and biochemistry, together with its treatment and prevention.

The greater part of the book is devoted to kwashiorkor in children; the condition in the adult may not necessarily be exactly the same disease. With most of the disorders of the temperate zone well described it must have been a great thrill to the authors to find such a common disease to investigate, and they are to be congratulated on presenting such a readable and scientific account of their researches.

The book is well illustrated and produced, and it is important that paediatricians should be well informed of the disease because of the nutritional principles involved.